Report on the Deliberation Results

May 20, 2021

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Vaxzevria Intramuscular Injection
Non-proprietary Name	COVID-19 (SARS-CoV-2) Vaccine (Recombinant Chimpanzee Adenovirus Vector)
Applicant	AstraZeneca K.K.
Date of Application	February 5, 2021

Results of Deliberation

Under the current pandemic of disease caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), the applicant has submitted an application for approval of the product on the understanding that the product is qualified for approval based on Article 14-3, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as the "Pharmaceuticals and Medical Devices Act").

In its meeting held on May 20, 2021, the Second Committee on New Drugs discussed whether the product was qualified for Special Approval for Emergency under Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The Committee concluded that the product may be approved with the conditions listed below, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since there is limited information 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 schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.
3. Results of the ongoing or scheduled Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.
4. The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is limited information on the long-term stability, etc., at the current moment of the approval. Therefore, after the market launch, the applicant is required to continue to collect and report the information.
5. The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to appropriately instruct physicians to 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 who have provided written informed consent through the vaccine screening questionnaire in advance.
6. Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 6 months after the approval. If new data, etc., submitted in accordance with the approval conditions necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

Report on Special Approval for Emergency

May 13, 2021
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	Vaxzevria Intramuscular Injection
Non-proprietary Name	COVID-19 (SARS-CoV-2) Vaccine (Recombinant Chimpanzee Adenovirus Vector)
Applicant	AstraZeneca K.K.
Date of Application	February 5, 2021
Dosage Form/Strength	Injection: each vial contains 5×10^{11} viral particles of COVID-19 (SARS-CoV-2) Vaccine (recombinant chimpanzee adenovirus vector) as an active ingredient
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Items Warranting Special Mention	The product is handled as a product that requires approval from the Minister of Health, Labour and Welfare prescribed in Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 1 of the Act.
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

Two separate doses of 0.5 mL each should be administered intramuscularly at a 4- to 12-week interval.

Approval Conditions and Other Requirements

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item 1

   The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is limited information on the long-term stability, etc., at the current moment of the approval. Therefore, after the market launch, the applicant is required to continue to collect and report the information.
   (2) Matters related to Item 2

   When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.
   (3) Matters related to Item 3

   The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to vaccine recipients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.
   (4) Matters related to Item 4

   The applicant is required to report the quantity of the product sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
   (1) The applicant is required to develop and appropriately implement a risk management plan.
   (2) Since there is limited information on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.
   (3) Results of the ongoing or scheduled Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.

(4) The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is limited information on the long-term stability, etc., at the current moment of the approval. Therefore, after the market launch, the applicant is required to continue to collect and report the information.

(5) The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to appropriately instruct physicians to 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 who have provided written informed consent through the vaccine screening questionnaire in advance.

(6) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 6 months after the approval. If new data, etc., submitted in accordance with the approval conditions necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

3. The product is approved based on Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The approval may be withdrawn in accordance with the provision in Article 75-3 of the Act in a case where (a) the product does not conform to one or more Items of Article 14-3, Paragraph 1 of the Act or (b) the withdrawal is necessary to prevent the emergence or expansion of public health risks.

Attachment

Report on Special Approval for Emergency (1)

April 8, 2021

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	Vaxzevria Intramuscular Injection
Non-proprietary Name	COVID-19 (SARS-CoV-2) Vaccine (Recombinant Chimpanzee Adenovirus Vector)
Applicant	AstraZeneca K.K.
Date of Application	February 5, 2021
Dosage Form/Strength	Injection: each vial contains 5×10^{11} viral particles of COVID-19 (SARS-CoV-2) Vaccine (recombinant chimpanzee adenovirus vector) as an active ingredient
Proposed Indication	Prevention of disease caused by SARS-CoV-2 infection (COVID-19)

Proposed Dosage and Administration

The usual adult dosage is 2 separate doses of 0.5 mL each administered intramuscularly at a 4- to 12-week interval.

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List of Abbreviations

See Appendix.

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

Coronaviruses are positive-sense, single-stranded RNA viruses belonging to the family Coronaviridae in the order Nidovirales. In the past, 4 types of coronaviruses have been known to infect humans through casual contact and cause common cold: HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1. In recent years, severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) have been identified in 2003 and 2012, respectively, as coronaviruses that infect humans from animals and cause severe pneumonia.

On December 31, 2019, it was reported to WHO that a pneumonia of unknown cause occurred in Wuhan City, Hubei Province of China. On January 12, 2020, WHO announced that the pneumonia was caused by a novel coronavirus (https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/ [last accessed on April 6, 2021]). On January 30, 2020, WHO announced that the occurrence status of the novel coronavirus-associated pneumonia in Wuhan City, Hubei Province of China falls under the category of public health emergency of international concern [1)] (https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov) [last accessed on April 6, 2021]). On February 11, 2020, the novel coronavirus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease caused by SARS-CoV-2 was named corona virus disease (COVID-19) (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it [last accessed on April 6, 2021]). As of April 4, 2021, the total number of people infected is 130,459,184 and the total number of deaths is 2,842,325 in the world. The following are regional percentages of infection cases and deaths of the total global numbers (according to the WHO regional classification): 43% (infection cases) and 48% (deaths) in Americas; 35% and 34% in Europe, 11% and 7% in South-Eastern Asia; 5% and 5% in Eastern Mediterranean; 2% and 2% in Africa; and 1% and 1% in Western Pacific. (https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---6-april-2021 [last accessed on April 6, 2021]).

In Japan, on January 15, 2020, the first patient with SARS-CoV-2-related pneumonia was confirmed. On February 1, 2020, COVID-19 [2)] was classified as a Designated Infectious Disease [3)] pursuant to the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Act No. 114 of 1998) (Infectious Diseases Control Act) and as a Quarantinable Infectious Disease [4)] pursuant to the Quarantine Act (Act No. 201 of 1951). On April 7, 2020, the Japanese government issued the first declaration of a state of emergency based on the amended Act on Special Measures for Pandemic Influenza and New Infectious Diseases Preparedness and Response (Act No. 31 of 2012); the declaration was lifted on May 25, 2020. [5)] On January 7, 2021, the government issued the second declaration of a state of emergency, which was lifted on March 22,

1) The term Public Health Emergency of International Concern is defined as follows in the International Health Regulations of WHO:
   (a) An extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease
   (b) An extraordinary event which is determined to potentially require a coordinated international response
2) Limited to the disease caused by the novel coronavirus of genus Betacoronavirus that was reported as “transmissible to humans” from the People's Republic of China to WHO in January 2020
3) The term Designated Infectious Disease means already known infectious diseases (excluding Class I Infectious Diseases, Class II Infectious Diseases, Class III Infectious Diseases, and Novel Influenza Infection, etc.) specified by Cabinet Order as a disease which would be likely to seriously affect the health of the public in the event of its spread if the provisions of the Infectious Diseases Control Act, in whole or in part, did not apply mutatis mutandis (Article 6 of the Infectious Diseases Control Act).
4) The term Quarantinable Infectious Disease means diseases specified by Cabinet Order as those which require inspection in order to prevent pathogens of infectious diseases not endemic to Japan from entering the country (Article 2, Item 3 of the Quarantine Act).
5) Initially, the state of emergency was limited to Saitama, Chiba, Tokyo, Kanagawa, Osaka, Hyogo, and Fukuoka prefectures, but temporarily expanded to cover the whole Japan.

2021. [6)]

As of April 6, 2021, the cumulative number of people infected with SARS-CoV-2 in Japan is 485,085 and the number of deaths is 9,246. In addition, 2,445 cases of infection and 3 cases of death were confirmed in airport/seaport quarantine inspections and 15 cases of infection were confirmed among individuals returning from overseas via charter flights (https://www.mhlw.go.jp/stf/newpage_17903.html [last accessed on April 6, 2021]).

The initial symptoms of COVID-19 are similar to those of influenza and common cold, and it is difficult to distinguish them at an early stage after the onset. The incubation period from the exposure to SARS-CoV-2 to the onset is 1 to 14 days, and it usually takes about 5 days until the onset. (https://www.who.int/publications/i/item/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations [last accessed on April 6, 2021]). Patients with COVID-19 become infectious before symptom onset and especially highly infectious early after the onset. Further, some patients are asymptomatic. This is considered to be the cause of community transmission, making it difficult to control the transmission. Many patients present with symptoms including pyrexia, cough, malaise, dyspnea, taste disorder, and dysosmia. Approximately 80% of patients have mild symptoms and recover within approximately 1 week, approximately 20% of patients experience aggravated pneumonia symptoms, approximately 5% of patients progress to acute respiratory distress syndrome or multi-organ failure that requires ventilator support, and approximately 2% to 3% of patients die (*JAMA.* 2020; 323:1239-42). As of March 2, 2021, remdesivir is a drug approved in Japan for the treatment of COVID-19 and dexamethasone can be used within the range of approved indications. Despite the use of these treatments, the reported numbers of people infected, severe cases, and deaths in Japan are continuously increasing, and the tightness of the medical system is also becoming a problem. For these reasons, the prevention of COVID-19 by SARS-CoV-2 vaccines is expected as a measure against the spread of infections, and early development of vaccines is in demand. As of March 2021, in Japan, Comirnaty Intramuscular Injection (Pfizer Japan Inc.) has been approved as a vaccine for prevention of COVID-19, but prompt supplies of multiple types of vaccines are in demand due to the scale of SARS-CoV-2 infection, persistent and rapid spread of infections, the overwhelming effects of the pandemic on medical care and the society and economy, and the issue on supply quantity associated with vaccinations on a global scale.

Vaxzevria is a non-replicating recombinant chimpanzee adenovirus vector vaccine that encodes the S protein of SARS-CoV-2. For Vaxzevria, the chimpanzee adenovirus vector is used because many humans have already acquired immunity against human adenovirus serotypes and there is a concern that viral vectors using human adenovirus would not induce immune responses. The S protein subunit selected as the target antigen binds to the cellular receptor ACE2 via the receptor-binding domain and induces a virus-cell membrane fusion. Vaxzevria contains the nucleic acid sequence of the recombinant S protein that has been inserted into the ChAdOx1 viral vector, and does not contain other SARS-CoV-2 components. Neither transgenes nor gene products of the S protein are toxic or pathogenic, and neither of them contribute to viral vector replication or recombination.

6) The state of emergency covered Tokyo, Kanagawa, Saitama, Chiba, Osaka, Hyogo, Kyoto, Aichi, Gifu, Fukuoka, and Tochigi Prefectures.

Outside Japan, the development of Vaxzevria was initiated by the University of Oxford in UK for the purpose of preventing COVID-19, and 5 foreign clinical studies (Studies COV001, COV002, COV003, COV004, and COV005) are ongoing, sponsored by the University of Oxford (as of the end of March 2021), but the development has been transferred from the University of Oxford to AstraZeneca PLC. In Japan, a Japanese clinical study (Study D8111C00002) was initiated by AstraZeneca K.K. in August 2020, and the study is ongoing as of the end of March 2021.

Based on the data on the COVID-19-preventing effect and safety from pooled analyses of the 4 foreign clinical studies (Studies COV001, COV002, COV003, and COV005), the temporary authorization for the prevention of COVID-19 was granted in UK on December 29, 2020, and conditional approval was granted in EU on January 29, 2021.

Since the conditional approval was recently granted in EU and part of the results of Japanese Study D8111C00002 (which evaluated the immunogenicity and safety) was obtained, AstraZeneca K.K in Japan filed an application for marketing approval on February 5, 2021. The application was based on the results of pooled analyses of the 4 foreign clinical studies (Studies COV001, COV002, COV003 and COV005) as the pivotal data. Part of the results of Japanese Study D8111C00002 was submitted during this review.

The data submitted by the applicant was reviewed by PMDA based on “Handling of Drugs under Consideration for Special Approval for Emergency (Request)” (PSEHB/PED Notification No. 0401-1 dated April 1, 2021). The content of the review is presented in this report.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Vaxzevria is a non-replicating recombinant viral vaccine made by inserting the gene encoding the S-protein of SARS-CoV-2 into a replication-deficient chimpanzee adenovirus vector ChAdOx1 (AdvY25).

2.1 Active Substance

2.1.1 Generation and Control of Cell Substrates Used for Manufacturing of Raw Materials

HEK293 cells, which are the origin of master cell bank (MCB) used for manufacturing AZD1222, were transfected with adenovirus E1 gene when the cell line was established. Therefore E1 gene-deficient adenovirus can be replicated in the cells. HEK293 cells were genetically modified to generate the HEK293T-REx cell line, which stably expresses the TetR protein. This cell line was used to prepare MCB. Pre-working cell bank (pre-WCB) is prepared from MCB. WCB prepared from Pre-WCB is used for manufacturing AZD1222.

Purity tests and characterizations (cell type identification tests) were performed on MCB, Pre-WCB, WCB, and CAL in accordance with ICH Q5B and Q5D. The genetic stability in the cell bank system and during the manufacturing period was confirmed, and neither adventitious viruses nor non-viral adventitious agents were detected by the tests performed.

MCB, Pre-WCB, and WCB are stored in [redacted]. There is no plan to renew MCB. A new WCB is prepared from Pre-WCB as necessary.

2.1.2 Preparation and Control of Virus Seed

The virus seed used for manufacturing AZD1222 was prepared by introducing the S protein gene of SARS-CoV-2 with a tPA signal sequence into replication-deficient recombinant chimpanzee adenovirus lacking the E1 and E3 genes. HEK293T-REx cells grown in culture from Pre-WCB were infected with the virus seed as the origin. Then research virus seed, master virus seed (MVS), and working virus seed (WVS) were prepared in sequence.

MVS and WVS are stored at ≤[redacted]°C. There is no plan to renew MVS. A new WVS is prepared from MVS as necessary.

Characterization and purity tests shown in Table 1 were performed on MVS and WVS. In the manufacturing process at the time of preparation of MVS ([redacted]), the following were confirmed to be absent: *in vitro* adventitious viruses (bovine, porcine, and human), *in vivo* adventitious viruses ([redacted] and [redacted]), [redacted], mycobacteria, mycoplasma, replication competent adenovirus (RCA), [redacted], etc. In the manufacturing process at the time of preparation of WVS ([redacted]), the following were confirmed to be absent: [redacted], mycobacteria, mycoplasma, RCA, and [redacted].

Table 1 Characterization and Purity Tests of MVS and WVS

	Test	MVS	WVS
Characterization	Identification (PCR)	✓	✓
	Transgene sequence	✓	✓
	Total nucleotide sequence	✓	-
	Infectivity titer	✓	✓
	Vector particle concentration (qPCR)	✓	✓
Purity	Microbial limit	✓	✓
	Bacterial endotoxins	✓	✓

✓ = performed; - = not performed

2.1.3 Manufacturing Process

The manufacturing process of active substance consists of cell thawing, seed culture, bioreactor expansion culture, [redacted] and production culture, [redacted] and [redacted], [redacted], [redacted] chromatography, concentration and ultrafiltration, drug solution preparation, filtration and filling, freezing, storage, and testing. The active substance is stored at -90°C to -55°C in [redacted] container. Critical steps are [redacted] and [redacted], [redacted] and [redacted], [redacted], [redacted] chromatography, [redacted] and [redacted], [redacted], and [redacted].

The manufacturing process of active substance has been subjected to process validation at commercial scale.

2.1.4 Safety Evaluation of Adventitious Agents

Biological materials, namely HEK293T-REx cells (production cells) and a bovine milk-derived casein hydrolysate ([redacted]), are used in the manufacturing process of the active substance. Both of the biological materials have been shown to meet the Standards for Biological Ingredients.

At the time of preparation of MCB, the following tests were performed: sterility test, mycobacteria test, mycoplasma test, [redacted], contamination with virus-like particles, *in vitro* adventitious virus test ([redacted], [redacted], HEK293 cells), *in vivo* adventitious virus test ([redacted], [redacted], [redacted]), [redacted] virus test ([redacted]), [redacted] virus test ([redacted]), and [redacted] virus test (viruses specified in 9CFR [7)]). None of the tests showed contamination with adventitious agents.

The following tests were performed on the production culture media obtained at commercial scale: adventitious virus test, mycoplasma test, mycobacteria test, microbial limit test, test for absence of RCA, [redacted], and [redacted]. All of the tests were negative. The cell culture media for production are subjected to the following in-process control tests: adventitious virus test (*in vitro* and *in vivo*), microbial limit test, mycoplasma test, mycobacteria test, test for absence of RCA, [redacted], and [redacted].

2.1.5 Process Development

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

In some batches of the active substance made by Process (b), there was an error in the quantitative value of viral particle concentration due to excessive addition of polysorbate 80 in the process (see Section 11.5). This issue is discussed in the review section (see Section 2.R.2).

7) Bovine viral diarrhea virus, bovine adenovirus, bovine parvovirus, bluetongue virus, bovine RS virus, reovirus, rabies virus, and bovine parainfluenza virus (type 3) specified in 9CFR

Table 2 Major Changes in Manufacturing Process of Active Substance

Manufacturing process	Changes
From Process (a) [1] to Process (b) [2]	・ Change of [redacted] ・ Establishment of [redacted] and [redacted] ・ Change of [redacted] and scale-up of [redacted] ・ Elimination of [redacted] ・ Change of conditions for [redacted] ・ Introduction of [redacted] ・ Change of [redacted] ・ Change of [redacted] (change of [redacted]) ・ Change of [redacted] ([redacted])
From Process (b) to Process (c) [3]	・ Change of [redacted] ・ Scale-up of [redacted] ・ Change of conditions for [redacted] ・ Change of [redacted] (change of [redacted]) ・ Change of [redacted] ([redacted])
From Process (c) to Process (d) [4]	・ Change of [redacted] ・ Addition of [redacted] ・ Change of conditions for [redacted] ・ Change of conditions for [redacted] ・ Addition of [redacted] ・ Change of [redacted] (change of [redacted]) ・ Change of [redacted] ([redacted])

1) Active substance of [redacted], 2) Active substance of [redacted], 3) Active substance of [redacted], 4) Active substance of [redacted]

2.1.6 Characteristics

2.1.6.1 Structure, physicochemical and biological properties

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

Table 3 Outline of Characterizations

Item		
Structure	Primary structure	Transgene sequence (Sanger sequencing), S protein-expressing gene (qPCR), restriction enzyme mapping of viral genome genes, viral capsid protein profiling
	Viral particles	Shape (transmission electron microscopy), particle size variant (transmission electron microscopy, nanoparticle tracking analysis [NTA], molar molecular weight [FFF-MALS], spectroscopy A320/A260 ratio, ultracentrifugal analysis [AUC])
Biological properties		Infectivity titer (Immunostaining of adenovirus Hexon), immunoassay for S proteins binding to ACE2

2.1.6.2 Product-related substances/product-related impurities

Product-related impurities are aggregates of viral particles, fragments of viral particles, empty viral particles without inserted gene, viral particles with incomplete inserted gene, non-infectious viral particles, and RCA. Aggregates of viral particles, fragments of viral particles, empty viral particles without inserted gene, viral particles with incomplete inserted gene, and non-infectious viral particles are appropriately controlled with the specifications of active substance and vaccine product. RCA is appropriately controlled by in-process control tests of active substance.

2.1.6.3 Process-related impurities

Process-related impurities are Host Cell Impurity A, Host Cell Impurity B, Impurity C, Impurity D, Impurity E, and Impurity F. Host cell Impurity A, Host Cell Impurity B, and Impurity C are appropriately controlled by the specifications of active substance. Impurity D, Impurity E, and Impurity F are all removed constantly in the manufacturing process.

2.1.7 Control of Active Substance

The specifications of active substance include description, identification (qPCR), osmotic pressure, pH test, DNA:protein ratio, viral particle:infectious viral particle ratio, Impurity C, Host Cell Impurity A (qPCR), Host Cell Impurity B (ELISA), bacterial endotoxins, microbial limit, biological activity (infectivity titer), polysorbate 80, and assay (viral particle concentration).

2.1.8 Stability of Active Substance

Stability tests of active substance are shown in Table 4.

Table 4 Stability Tests of Active Substance (as of March 2021)

	Storage condition	Manufacturing process	Number of batches	Test period	Storage form
Long-term [1)]	-90°C to -55°C	Process (c) [2)]	2	4 months	[redacted] container
			1	3 months	
		Process (d) [3)]	3	2 months	[redacted] container
			3	1 month	
	5 ± 3°C	Process (c)	1	6 months	[redacted] container
			2	4 months	
		Process (d)	4	2 months	[redacted] container
			2	1.5 months	
Accelerated	25 ± 2°C/60 ± 5% RH	Process (c)	3	2 months	[redacted] container
		Process (d)	3	2 months	[redacted] container

1) Long-term tests (-90°C to -55°C and 5 ± 3°C) are ongoing and continued until 12 months.
2) Active substance of [redacted], 3) Active substance of [redacted]

The long-term testing showed no obvious changes in quality attributes of the active substances made by Processes (c) and (d) throughout the test period, demonstrating the conformity to the specifications (for shelf lives, see Section 2.R.1).

2.2 Vaccine Product

2.2.1 Description and Composition of Vaccine Product and Formulation Development

Vaxzevria is a vial product containing AZD1222 at a concentration of 1×10^{11} vp/mL per vial. Each vial is designed to deliver 10 doses. The labeled volume is 5 mL, but the vial contains an overfill to allow the extraction of 10 doses. The vaccine product contains excipients: L-histidine/L-histidine hydrochloride hydrate, sodium chloride, magnesium chloride, disodium edetate hydrate, sucrose, polysorbate 80, ethanol, and water for injection. The primary container consists of a glass vial (10 mL volume) and a bromobutyl rubber stopper. The secondary package is a paper box.

2.2.2 Manufacturing Process

The manufacturing process of vaccine product consists of receipt and storage of active substance, thawing, [redacted] and mixing, bioburden reduction filtration, mixing, aseptic filtration, aseptic filling, stoppering and capping, visual inspection, labeling, packaging, and storage. The vaccine product is stored in a glass vial at 2°C to 8°C. Critical steps are [redacted] and mixing, [redacted], [redacted], and [redacted] and [redacted].

The manufacturing process of vaccine product has been subjected to process validation at commercial scale.

2.2.3 Process Development

Table 5 shows major changes made to the manufacturing process during the development of vaccine product. The vaccine product made by Process A, B, or C was used in clinical studies. Processes A, B, and C contain the active substances made by Processes (a), (b), and (c), respectively. The to-be-marketed vaccine product is made by Process D, and contains the active substance made by Process (d). For each change of the manufacturing process, the pre-change and post-change vaccine products were shown to have comparable quality attributes by batch analysis and characterization.

In some batches of the vaccine product made by Process B, there was an error in the quantitative value of viral particle concentration due to excessive addition of polysorbate 80 to the active substance made by Process (b) (see Section 11.5). This issue is discussed in the review section (see Section 2.R.2).

Table 5 Major Changes in Manufacturing Process of Vaccine Product

Manufacturing process	Changes
From Process A [1)] to Process B [2)]	・ Change of and change of ・ Change of ・ Change of ・ Change of ( )
From Process B to Process C [3)]	・ Change of and change of ・ Change of ・ Change of ( ) ・ Change of ( )
From Process C to Process D [4)]	・ Change of ・ Change of ( )

1) Vaccine product of , 2) Vaccine product of , 3) Vaccine product of , 4) Vaccine product of

2.2.4 Control of Vaccine Product

The specifications of vaccine product include description, identification (qPCR), osmotic pressure, pH test, DNA:protein ratio, viral particle:infectious viral particle ratio, foreign insoluble matters, insoluble particulate matters, extractable volume, bacterial endotoxins, sterility test, biological activity (infectivity titer), polysorbate 80, and assay (viral particle concentration).

2.2.5 Stability of Vaccine Product

Major stability tests of vaccine product are summarized in Table 6.

Table 6 Stability Tests of Vaccine Product (as of March 2021)

	Storage condition	Manufacturing process of active substance	Manufacturing process of vaccine product	Number of batches	Test period	Storage form
Long-term [1)]	5 ± 3°C, inverted	Process (c) [2)]	Process C [4)]	3	6 months	Glass vial, bromobutyl rubber stopper
		Process (d) [3)]	Process D [5)]	3	0 months	
Accelerated	25 ± 2°C/60 ±5% RH, inverted	Process (c)	Process C	3	2 months	
		Process (d)	Process D	3	0 months	

1) Long-term tests are ongoing and continued until 12 months.
2) Active substance of , 3) Active substance of , 4) Vaccine product of , 5) Vaccine product of

In the long-term testing of the vaccine product made by Process C, biological activity (infectivity titer) showed a slightly decreasing trend but conformed to the specifications. The other quality attributes of the vaccine product made by Process C, showed no obvious change throughout the test period, demonstrating the conformity to the specifications. The results of long-term testing of vaccine product made by Process D are not available at present.

The results of ongoing tests are described in Report (2) (for shelf lives, see Section 2.R.1).

2.R Outline of the review conducted by PMDA

Based on the data submitted to date and the following review, PMDA concluded that there were no critical quality problems that may affect the evaluation of nonclinical and clinical study results of Vaxzevria. PMDA instructed the applicant to promptly submit the results of ongoing long-term testing of active substance and vaccine product. The review results is described in Report (2).

2.R.1 Shelf lives of active substance and vaccine product

The applicant proposed a shelf life 6 months at -90°C to -55°C for active substance and a shelf life of 6 months at 5 ± 3°C for vaccine product. These shelf lives are similar to those established in foreign countries.

The applicant's explanation about the proposed shelf lives:
The results of quality tests demonstrated the comparability between the active substances made by Processes (c) and (d).

As for the shelf life of active substance, the long-term testing of active substances made by Processes (c) and (d) (3 and 6 batches, respectively) are ongoing (-90°C to -55°C and 5 ± 3°C for both). There have been no significant changes in major quality attributes (description, pH, infectivity titer, viral particle concentration, viral particle:infectious viral particle ratio, etc.) by 4 months for active substance made by Process (c) and by 2 months for active substance made by Process (d). Data will be obtained until 12 months from the long-term testing of active substances made by Processes (c) and (d).

As for the shelf life of vaccine product, there have been no significant changes in major quality attributes (description, pH, infectivity titer, viral particle concentration, viral particle:infectious viral particle ratio, etc.) by 6 months in the long-term testing of 3 batches of vaccine product made by Process C. The results of long-term testing of vaccine product made by Process D are not available at present. However, a shelf life of 6 months is also applicable for vaccine product made by Process D, because vaccine products made by Processes C and D were shown to be comparable by quality tests. The long-term testing of vaccine product made by the Process D is ongoing, and data will be obtained until 12 months.

PMDA's view:
No major problems in stability have been identified in the currently available data from the long-term testing of 3 batches of active substances made by Processes (c) and (d) and the long-term testing of vaccine product made by Process C. However, 6-month stability data should be confirmed when setting the shelf lives of active substance and vaccine product. The shelf lives will be established after confirming the results of the ongoing long-term testing, and will be described in Report (2).

2.R.2 An error in the quantitative value of viral particle concentration that occurred due to excessive addition of polysorbate 80

An error was identified in the quantitative value of viral particle concentration measured by spectrophotometry in some batches of vaccine product made by Process B.

The applicant's explanation:

The viral particle concentration in the vaccine product used in the foreign clinical study (Study COV002) was measured by spectrophotometry. Viral particle concentration in vaccine product made by Process B, was measured by both spectrophotometry and qPCR; in some batches of the vaccine product, values measured by spectrophotometry were approximately 2.3 times higher than those measured by qPCR (see Section 11.5). To elucidate its cause, the method of spectrophotometry was examined. The results revealed that polysorbate 80 interfered with the absorbance, thereby showing a higher viral particle concentration than the actual value. In addition, the content of polysorbate 80 in the batches was approximately twice that in vaccine products made by Processes A and C. The cause of the error was an excessive amount of polysorbate 80 added by mistake to the active substance (contained in the batches concerned) during the drug solution preparation process. To address this issue, qPCR was used to measure the viral particle concentration in subsequent active substance made by Process (b) and vaccine product made by Process B, because qPCR is not affected by the content of polysorbate 80. Based on the qPCR results, the dose for clinical studies (5×10^{10} vp) was determined. Spectrophotometry was performed to measure the viral particle concentrations in active substances made by Processes (a) and (c) and vaccine products made by Processes A and C, and polysorbate concentrations in the active substances and vaccine products were not enough to interfere with the spectrophotometry. Further, qPCR was performed to measure the viral particle concentrations in active substances made by Processes (a), (b), and (c), and vaccine products made by Processes A, B, and C; the results showed no differences between the active substances or between the vaccine products.

The applicant decided to use anion exchange chromatography, instead of spectrophotometry, to measure viral particle concentrations in the proposed manufacturing process (active substance made by Process (d) and vaccine product made by Process D), because anion exchange chromatography can separate polysorbate 80 and viral particles. The anion exchange chromatography-measured viral particle concentrations in active substances made by Processes (b), (c), and (d), met the same specifications, and those in vaccine products made by Processes A, B, C, and D met the same specifications. Infectivity titer per viral particle was measured for all manufacturing processes, showing no major differences in infectivity titer per viral particle between the active substances or between the vaccine products.

PMDA's conclusion:

The viral particle concentrations in the vaccine product containing excessive polysorbate 80 are considered to be equivalent to those in other vaccine products, as shown by the re-measurement by qPCR and anion exchange chromatography. The proposed manufacturing process can appropriately control viral particle concentrations because it uses anion exchange chromatography, which is not affected by polysorbate 80. In addition, the dose used as SD dose in clinical studies (see Section 11.5) is considered to be the same as the labelled dose, judging

from the results of re-consideration or re-measurement of the method of measuring viral particle concentrations, in addition to the comparability between manufacturing processes.

2.R.3 New excipients

Vaxzevria (vaccine product) contains magnesium chloride in an amount exceeding the amounts contained in previously approved products for intramuscular administration. PMDA concluded that there were no particular problems with magnesium chloride contained in Vaxzevria based on the following review.

2.R.3.1 Specifications and stability

Based on the submitted data, PMDA concluded that there were no particular problems with the specifications and stability of magnesium chloride.

2.R.3.2 Safety

Based on the submitted data, PMDA concludes that the amount of magnesium chloride used in the proposed vaccine product is unlikely to raise safety issues.

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

3.1 Primary Pharmacodynamics

3.1.1 Mouse Immunogenicity Study (CTD 4.2.1.1.2)

The immunogenicity of Vaxzevria against SARS-CoV-2 was assessed after single-dose intramuscular administration of Vaxzevria or ChAdOx1 GFP (6×10^9 vp/body each) to BALB/c mice (Vaxzevria group, 5 females; control group, 3 females) and CD1 mice (Vaxzevria group, 8 females; control group, 3 females). The results were as follows:

[1] Investigation of specific IgG antibodies against the S protein S1 and S2 (ELISA)
When IgG antibodies were measured using the sera from each group 14 days after administration of Vaxzevria, the results showed the production of antibodies specific to S1 and S2 in both Vaxzevria groups.

[2] Investigation of neutralizing antibodies against SARS-CoV-2 (neutralizing antibody analysis using live virus)
When neutralizing antibodies against SARS-CoV-2 [8)] were measured using the sera from each group 9 days after administration of Vaxzevria, the results showed the production of neutralizing antibodies against SARS-CoV-2 in both Vaxzevria groups.

[3] Investigation of IgG subclasses (ELISA)
When IgG subclasses (IgG1, IgG2a, IgG2b, and IgG3) were measured using the sera from each group 14

8) nCoV-WA1/2020 strain: This virus strain was isolated in Washington State, US in January 2020 from an oropharyngeal swab of a patient who developed COVID-19 after returning from Wuhan, China. No amino acid mutation from the Wuhan-Hu-1 strain was observed, and the infectivity is assumed to be equivalent to that of the Wuhan-Hu-1 strain.

days after administration of Vaxzevria, the results showed Th1-related increases in IgG2a and IgG2b in both Vaxzevria groups.

[4] Investigation of cytokine production in spleen cells (ELISpot and intracellular cytokine staining)
When the spleen cells from each group were stimulated with the full-length S protein, S1 or S2 peptide 14 days after administration of Vaxzevria, the results showed Th1-related increases in IFN-γ producing cells. In addition, the Vaxzevria groups showed increases in CD3+ T cells that produce IFN-γ or TNF-α, with no increases in CD3+ T cells that produce Th2-related IL-4 or IL-10.

3.1.2 Porcine Immunogenicity Study (CTD 4.2.1.1.7)

Vaxzevria-induced immune response to SARS-CoV-2 was evaluated after single-dose or 2-dose (28-day interval) intramuscular administration of Vaxzevria (5.12×10^{10} vp/body) to pigs (Vaxzevria group, 3 females). The results were as follows:

[1] Investigation of specific IgG antibodies and neutralizing antibodies against the S protein (ELISA and neutralizing antibody analysis using pseudovirus)
When specific IgG antibodies in the serum and neutralizing antibodies against SARS-CoV-2 pseudovirus were measured after single-dose or 2-dose administration of Vaxzevria, the results showed the detection of both types of antibodies from 14 days after administration of Vaxzevria and increases in the antibodies due to 2-dose administration.

[2] Investigation of cytokine production and T-cell response using peripheral blood mononuclear cells (ELISpot and intracellular cytokine staining)
When the peripheral blood mononuclear cells from each group were stimulated with S protein peptide pools 14, 28, or 42 days after administration of Vaxzevria, the results showed increases in IFN-γ and responses of CD4+ and CD8+ T cells (increases in intracellular cytokines).

3.1.3 Simian Challenge Study (CTD 4.2.1.1.2, 4.2.1.1.4)

Vaxzevria-induced immune response and the effect of Vaxzevria in preventing disease caused by SARS-CoV-2 were evaluated after single-dose (Vaxzevria group, 6 animals; control group, 5 animals) or 2-dose (28-day interval) (Vaxzevria group, 6 animals; control group, 1 animal) intramuscular administration of Vaxzevria (2.5×10^{10} vp/body) or ChAdOx1 GFP (2.5×10^{10} vp/body) to rhesus monkeys (CTD 4.2.1.1.2), and after single-dose intramuscular administration of Vaxzevria (2.5×10^{10} vp/ body) or PBS (CTD 4.2.1.1.4) to rhesus monkeys (Vaxzevria group and control group, 6 animals each). Based on the following results, the applicant explained that Vaxzevria was shown to have an effect in preventing SARS-CoV-2.

[1] Investigation of S-protein-specific IgG antibodies and neutralizing antibodies (ELISA and neutralizing antibody analysis using live virus) (CTD 4.2.1.1.2)
When S-protein-specific antibodies and neutralizing antibodies against SARS-CoV-2 [8)] were measured

immediately before the exposure to SARS-CoV-2 of Vaxzevria (28 days after single-dose or 2-dose administration) using the sera from each group, the results showed Vaxzevria-induced production of both types of antibodies (Table 7).

Table 7 RBD-specific IgG Antibodies and Neutralizing Antibodies in Serum Immediately before Exposure to SARS-CoV-2 after Administration of Vaxzevria

Group	RBD-specific IgG antibody titer GMT [2-sided 95% CI]	Neutralizing antibody titer GMT [2-sided 95% CI]
Single-dose	955 [447, 2041]	15 [9, 26]
2-dose	4365 [1698, 11482]	52 [24, 115]
Control	50	3

[2] Investigation of cytokine production in peripheral blood mononuclear cells (ELISpot and intracellular cytokine staining) (CTD 4.2.1.1.2)

Twenty-eight days after single-dose or 2-dose administration of Vaxzevria, animals from each group were exposed intranasally, intratracheally, intraorally, or intraocularly to SARS-CoV-2 (2.6×10^6 $TCID_{50}$). Then, peripheral blood mononuclear cells collected from the animals 1-7 days after the exposure were stimulated with the full-length S protein. The results showed increases in IFN-γ 1 day after the exposure in the Vaxzevria groups. On the other hand, no differences were observed between the Vaxzevria groups and the control group (ChAdOx1 GFP treatment group) in TNF-α, IL-2, IL-4, IL-5, IL-6, IL-10, and IL-13.

[3] Investigation of the disease-preventing effect after the exposure to SARS-CoV-2

1) Residual viral RNA, clinical signs, lung histopathological findings (CTD 4.2.1.1.2)

Twenty-eight days after single-dose or 2-dose administration of Vaxzevria, animals from each group were exposed intranasally, intratracheally, intraorally, or intraocularly to SARS-CoV-2 [8] (2.6×10^6 $TCID_{50}$). The results for residual viral RNA, lung histopathological findings, and clinical sign scores are shown in Table 8.

Table 8 Residual Viral RNA, Lung Histopathological Findings, and Clinical Sign Scores after Exposure to SARS-CoV-2

Endpoint	Vaxzevria (single-dose)	Vaxzevria (2-dose)	Control [a]
Residual viral RNA (bronchoalveolar lavage fluid and lung tissue) [b]	Bronchoalveolar lavage fluid: 1/6 animals on Day 3; 0/6 animals on Day 5 Lung tissue: 2/6 animals on Day 7	Bronchoalveolar lavage fluid: 1/6 animals on Day 3; 0/6 animals on Day 5 Lung tissue: 2/6 animals on Day 7	Bronchoalveolar lavage fluid: 6/6 animals on Day 3; 5/6 animals on Day 5 Lung tissue: 6/6 animals on Day 7
Lung histopathological findings [d]	0/6 animals	0/6 animals	2/3 animals [e]
Clinical sign scores [c] (Mean [2-sided 95% CI])	7.5 [5.0, 10.0] on Day 3; 1.8 [0.3, 3.4] on Day 5; 2.0 [0.9, 3.1] on Day 7	8.8 [7.3, 10.3] on Day 3; 6.3 [3.5, 9.1] on Day 5; 7.5 [5.8, 9.2] on Day 7	12.5 [10.8, 14.2] on Day 3; 9.3 [6.9, 11.7] on Day 5; 9.5 [6.6, 12.4] on Day 7

a) Control: ChAdOx1 GFP
b) Viral RNA: Bronchoalveolar lavage fluid was collected 3 and 5 days after virus exposure and lung tissue was collected 7 days after virus exposure to assess gRNA-positive animals.
c) Clinical signs scores: After exposure to SARS-CoV-2, the systemic conditions, skin and fur conditions, secretions, respiration, fecal and urinary conditions, appetite, and activity were assessed.
d) Samples were collected 7 and 13 or 14 days after viral exposure to assess the number of animals with lung disorders.
e) Viral interstitial pneumonia was observed.

2) Residual viral RNA, lung histopathological findings, and CT scores (CTD 4.2.1.1.4)

Twenty-seven days after single-dose administration of Vaxzevria, animals from each group were exposed intranasally or intratracheally to SARS-CoV-2.[9] The results for residual viral RNA, lung histopathological findings, and CT scores are shown in Table 9.

Table 9 Residual Viral RNA, Lung Histopathological Findings, and CT Scores after Exposure to SARS-CoV-2

Endpoint	Group	Measurement time points		
		7 days after exposure	13 days after exposure	14 days after exposure
Residual viral RNA [b)] in bronchoalveolar lavage fluid	Vaxzevria	0/2 animals	0/2 animals	0/2 animals
	Control [a)]	2/2 animals	1/2 animals	0/2 animals
Residual viral RNA[c)] in lung tissue	Vaxzevria	1/2 animals	0/4 animals	
	Control [a)]	2/2 animals	3/4 animals	
Lung histopathological findings [d)]	Vaxzevria	0/2 animals	0/4 animals	
	Control [a)]	1/2 animals	1/4 animals	
		5 days after exposure	12 days after exposure	
CT scores [e)] (Mean [2-sided 95% CI])	Vaxzevria	7.5 [6.3, 8.7]	8.3 [4.7, 11.9]	
	Control [a)]	17.8 [13.4, 22.1]	7.0 [3.7, 10.3]	

a) Control: PBS
b) Animals positive for viral RNA in bronchoalveolar lavage fluid were assessed with qPCR, 7, 13, and 14 days after virus exposure.
c) Animals positive for viral RNA in lung tissue were assessed with ISH, 7 and 13 or 14 days after virus exposure.
d) Samples were collected 7 and 13 or 14 days after viral exposure to assess the number of animals with lung disorders.
e) CT scores: Ground-glass opacity, infiltrative shadow, findings associated with reticular shadow within ground-glass opacity, presence/absence and distribution of nodular and peripheral lobular infiltrative shadow, and pulmonary embolism were assessed.

3.1.4 Ferret Challenge Study (CTD 4.2.1.1.6)

Vaxzevria-induced immune response and the effect of Vaxzevria in preventing disease caused by SARS-CoV-2 were evaluated after single-dose or 2-dose (28-day interval) intramuscular administration of Vaxzevria (2.5×10^{10} vp/body) or ChAdOx1 GFP (2.5×10^{10} vp/body) or single-dose intramuscular administration of formalin-inactivated SARS-CoV-2 (containing alum adjuvant) to ferrets (Vaxzevria group, 4 or 6 females; control group, 2 females; inactivated SARS-CoV-2 group, 6 animals). Based on the following results, the applicant explained that Vaxzevria was shown to have a certain effect in preventing disease caused by SARS-CoV-2.

[1] Investigation of neutralizing antibodies using SARS-CoV-2 (PRNT assay)

When neutralizing antibodies against SARS-CoV-2 [9)] were measured over time using the sera from each group after single-dose or 2-dose administration of Vaxzevria, the results showed the production of neutralizing antibodies with single-dose administration and transient increases in neutralizing antibodies with 2-dose administration.

[2] Investigation of prevention of infection/disease after the exposure to SARS-CoV-2

Twenty-eight days after single-dose or 2-dose administration of Vaxzevria, animals from each group were exposed intranasally to SARS-CoV-2 [9)] (5×10^6 PFU/body), and viral RNA levels in nasal lavage fluid, pharyngeal swab, and blood were measured over time up to 15 days after the exposure. In nasal lavage fluid and pharyngeal swab, viral RNA levels were lower in the Vaxzevria group than in the control group and inactivated SARS-CoV-2 group. On the other hand, viral RNA was not detected in blood in any of the groups.

When histopathological examination of the lungs was performed 14 days after the intranasal exposure to SARS-CoV-2, inflammatory lesions were observed in all groups, and histopathological scores are shown in Table 10.

9) Australia/VIC01/2020 strain: This virus strain was isolated from a nasopharyngeal swab of a patient who developed COVID-19 soon after arriving at Melbourne from Wuhan, China in January 2020. S247R mutation is present in the S protein, but the infectivity is assumed to be equivalent to that of the virus strain that became epidemic in the early stage.

Table 10 Histopathological Scores in the Lungs after Exposure to SARS-CoV-2

Item	Number of days after exposure to SARS-CoV-2	Vaxzevria		Control		Inactivated SARS-CoV-2
		Single-dose	2-dose	Single-dose	2-dose	Single-dose
Cumulative lung histopathological scores [a)] (Mean [2-sided 95% CI])	6 to 7 days	2.0	3.0	5.0 [2.2, 7.8]	8.0	12.0 [10.6, 13.4]
	13 to 15 days	4.0 [3.1, 4.9]	4.3 [3.4, 5.6]	6.0 [3.6, 6.4]	7.5 [6.8, 8.2]	5.5 [3.5, 7.5]

a) Lung histopathological scores: Inflammation with bronchial or bronchiolar exudation or infiltration of inflammatory cells, perivascular infiltration of inflammatory cells, and alveolar wall and alveolar space infiltration of inflammatory cells are assessed.

3.2 Safety Pharmacology (CTD 4.2.1.3.1)

Safety pharmacology studies to evaluate the effects of Vaxzevria on the cardiovascular and respiratory systems are summarized in Table 11. Effects on the central nervous system were assessed in a repeated-dose intramuscular toxicity study in mice (CTD 4.2.3.2.1). Based on the following results, the applicant explained that Vaxzevria has no effects on the physiological functions of the cardiovascular, respiratory, and central nervous systems.

Table 11 Summary of Safety Pharmacology Study Results

Test system	Test system	Endpoints	Dose (μL/body)	Route of administration	Major findings	Attachment CTD
Male mice (CD-1) (6 males/group)	Cardiovascular system	Blood pressure, heart rate, body temperature	0, 70 [a)]	Intramuscular	No effects	4.2.1.3
	Respiratory system	Respiratory rate, tidal volume, minute ventilation, etc.			No effects	

a) Vaxzevria (2.59×10^{10} vp/70 μL)

3.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA concluded that there were no particular problems with the nonclinical pharmacology of Vaxzevria.

3.R.1 Mechanism of action

The applicant's explanation about the mechanism of action of Vaxzevria:

After being administered intramuscularly, Vaxzevria is considered to infect the cells around the administration site, thereby making the S protein express in the infected cells. *In vivo* studies of Vaxzevria showed the production of neutralizing antibodies against SARS-CoV-2 (mice, pigs, monkeys, ferrets), Th1-dominant immune responses with increases in IgG2a and IgG2b (mice) and IFN-γ-producing CD8+ T cells (mice, pigs), and a certain level of efficacy in preventing disease caused by SARS-CoV-2 (monkeys, ferrets).

Based on the above study results, Vaxzevria is considered to induce the *in vivo* production of neutralizing antibodies against SARS-CoV-2 and Th1-dominant immune responses (humoral immunity and cellular immunity), thereby showing the effect in preventing disease caused by SARS-CoV-2.

PMDA accepted the applicant's explanation.

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

PMDA asked the applicant to explain the induction of neutralizing activity of Vaxzevria against SARS-CoV-2 variants that have been reported after the development of Vaxzevria.

The applicant's explanation:
As of January 14, 2021, the main strains prevalent in Japan are variants of B.1.1.284 and B.1.1.214 lineages.[10)] These 2 lineages are derived from variants that were prevalent in Europe between March and April 2020, and have no amino acid mutations affecting neutralizing activity of antibodies. On the other hand, the variants (B.1.1.7 lineage, B.1.351 lineage, B.1.1.248 lineage [P1 lineage]) reported between September and December 2020 in UK, South Africa, and Brazil, have also been detected in Japan since early December 2020 [11)]; there is a concern that all of these variants may avoid neutralizing antibodies.

Using sera from participants receiving 2 doses of Vaxzevria in Study COV001, neutralizing antibodies against B.1.1.7, B.1.1.248, and B.1.351 strains were measured to evaluate the induction of neutralizing activity of Vaxzevria against SARS-CoV-2 variants (see Section 7.1.2). The results showed that the neutralizing activity was 2.3 times lower for B.1.1.7 strain, 2.9 times lower for B.1.1.248 strain (P1 lineage), and 9 times lower for B.1.351 strain than for Victoria strain.[9)]

Preliminary assessment of SARS-CoV-2 variants that may affect the efficacy and immunogenicity of Vaxzevria is currently being conducted in collaboration between the University of Oxford and the University of the Witwatersrand. Assessment of neutralizing activity against emerging variants will also be conducted under a comprehensive virologic clinical surveillance plan (see Section 7.R.2.4).

PMDA accepted the applicant's explanation. The efficacy of Vaxzevria against variants is further discussed in Section 7.R.2.4.

3.R.3 Risk of disease enhancement

Animal studies of vaccines against SARS-CoV and MERS-CoV have shown that vaccination may have a risk of enhanced symptoms after viral infection (risk of disease enhancement), compared with non-vaccination. PMDA asked the applicant to explain the risk of disease enhancement associated with Vaxzevria.

The applicant explanation:
The risk of disease enhancement has also been reported with vaccines against not only SARS-CoV and MERS-CoV but also RSV, which causes respiratory diseases. It is likely to be caused by the production of antibodies without neutralizing activity and the presence of Th2-dominant immune responses that induce CD4 helper T cells with eosinophilic infiltration in the lungs (*Clin Vaccine Immunol.* 2016;23:189-95). However, animal studies showed that neutralizing antibodies against SARS-CoV-2 are produced and Th1-dominant humoral and

10) National Institute of Infectious Diseases: Novel Coronavirus SARS-CoV-2 Molecular Epidemiological Survey with Genomic Information (as of January 14, 2021) https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/2488-idsc/iasr-news/10152-493p01.html
11) National Institute of Infectious Diseases: Cases of new variants of novel coronavirus SARS-CoV-2 for which there are concerns about increased infectivity/transmission and changes in antigenicity in Japan (as of February 26, 2021). 152 cases of B.1.1.7 strain, 4 cases of B.1.351 strain, and 2 cases of B.1.1.248 strain have been reported in Japan.
https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/10221-covid19-37.html

cellular immunity are induced after vaccination with Vaxzevria. Furthermore, in challenge studies of Vaxzevria in rhesus monkeys and ferrets (see Sections 3.1.3 and 3.1.4), the exposure to SARS-CoV-2 did not exacerbate pneumonia with eosinophilic infiltration in the Vaxzevria groups compared with the control group.

Based on the above, Vaxzevria is considered to have a low risk of disease enhancement.

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

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

The results of a biodistribution study of Vaxzevria were submitted.

4.1 Biodistribution (CTD 4.2.2.3.6)

The distribution of Vaxzevria in various tissues, etc. was investigated after intramuscular administration to mice (Table 12).

Table 12 Biodistribution Study of Vaxzevria

Test system	Route of administration	Observation period	Dose (vp/animal)	Samples	Analytical techniques
Male and female mice (CD-1) (5 animals/sex/time point)	Intramuscular (left and right hindlimbs, 2 sites)	2, 3, 9, 29 days (blood and feces: 2, 3, 5, 9 days)	Vaxzevria 3.7×10^{10}	Administration site, inguinal lymph node, mesenteric lymph node, axillary lymph node, brain, spinal cord, sciatic nerve, heart, kidney, adrenal gland, liver, lung, testis, ovary, spleen, bone marrow, thymus, pancreas, mammary gland, blood, and feces	DNA fragments derived from Vaxzevria were measured by quantitative PCR using DNA extracted from each tissue as a sample, and the copy number per μg of DNA sample was calculated. The LLoQ of quantitative PCR was 50 copies/reaction.

The administration site and the adjacent sciatic nerve showed a high concentration of DNA fragments derived from Vaxzevria. The concentration was 10^4 to 10^7 copies/μg DNA (less than the quantitation limit in 1 of 30 samples) 2 days after administration, but tended to decrease over time, leading to 10^3 to 10^4 copies/μg DNA (less than the quantitation limit in 19 of 30 samples) 29 days after administration. Although at low concentrations, DNA fragments were noted in the bone marrow, liver, spleen, and lung (between less than the quantitation limit and 10^4 copies/μg DNA) 2 days after administration; the concentrations tended to decrease over time until 29 days after administration. In the following sites, DNA fragments were noted only in 1 to 2 samples during the observation period: the mammary gland (10^3 copies/μg DNA at 3 days after administration), inguinal lymph node (10^2 copies/μg DNA at 9 days after administration; 10^5 copies/μg DNA at 29 days after administration), mesenteric lymph node (10^2 copies/μg DNA at 3 days after administration), and feces (10^3 copies/μg DNA at 2 days after administration).

4.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA concluded that there is no particular concern about the biodistribution of Vaxzevria.

4.R.1 Biodistribution of Vaxzevria

The applicant's explanation about the biodistribution of Vaxzevria:

The distribution of DNA fragments derived from Vaxzevria was assessed in a biodistribution study in mice. The results showed that the distribution of AZD1222 was mostly limited to the administration site and adjacent tissues following intramuscular administration of Vaxzevria. The distribution of DNA fragments was also observed in tissues (bone marrow, liver, spleen, lung, etc.) other than the administration site, but the concentrations were lower than those in the administration site and the adjacent sciatic nerve, and tended to decrease over time. Even if temporarily distributed to tissues other than the administration site, Vaxzevria is assumed to disappear over time without replication or dissemination since it is a non-replicating virus.

PMDA accepted the applicant's explanation.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted results of toxicity studies (a repeated-dose toxicity study and a reproduction toxicity study) of Vaxzevria.

5.1 Single-Dose Toxicity

No single-dose toxicity studies of Vaxzevria have been conducted, but the single-dose (acute) toxicity of Vaxzevria was assessed based on the results obtained after the first dose in a repeated-dose intramuscular toxicity study in mice (CTD 4.2.3.2.1). No deaths from administration of Vaxzevria were reported, and edema at the administration site of Vaxzevria, body temperature increased (+0.47°C), etc. were observed.

5.2 Repeated-Dose Toxicity

A repeat-dose intramuscular toxicity study of Vaxzevria was conducted in mice (Table 13). The main findings were inflammatory changes at the administration site.

Table 13 Repeated-Dose Toxicity Study

Test system	Route of administration	Dosing period	Dose (μL/body)	Major findings	No observed adverse effect level (μL/body)	Attachment CTD
Male and female mice (CD-1)	Intramuscular	6 weeks (1 dose every 3 weeks: 3 doses in total [a]) + Recovery for 28 days	0 [b], 70 [c]	70 [d]: Body temperature increased, edema and inflammation at administration site[e] Reversibility: Yes	70	4.2.3.2.1

a) Administered at 35 μL/site in the left and right quadriceps muscles at 1, 22, and 43 days after the start of study
b) Aqueous solution containing 10 mM histidine, 7.5% [v/w] sucrose, 35 mM sodium chloride, 1 mM magnesium chloride, 0.1% polysorbate 80, 0.1 mM EDTA, and 0.5% [v/w] ethanol (pH 6.6)
c) Vaxzevria (3.7×10^{10} vp/70 μL)
d) Antibody production against the S protein was confirmed at 22, 43, and 74 days after the start of study.
e) Inflammation was observed around the sciatic nerve adjacent to the administration site, but according to a publication (*Toxicol Pathol.* 2020; 48:257-76), etc., it was judged to be a finding extended from inflammation at the administration site and specific to rodents as caused by the administration technique.

5.3 Genotoxicity

Since the ChAdOx1 vector used in Vaxzevria does not have the ability to be integrated into chromosomes, no genotoxicity studies of Vaxzevria have been conducted.

5.4 Carcinogenicity

Since Vaxzevria is not a medicinal product to be used for ≥6 months in clinical settings, no carcinogenicity studies of Vaxzevria have been conducted.

5.5 Reproduction Toxicity

A reproduction toxicity study was conducted in mice (Table 14). There were no effects of Vaxzevria on parent animals or offspring.

Table 14 Reproduction Toxicity Study

Type of study	Test system	Route of administration	Dosing period	Dose (μL/body)	Major findings	No observed adverse effect level (μL/body)	Attachment CTD
Fertility and early embryonic development to implantation; Embryo-fetal development; Pre- and postnatal development, including maternal function	Female mice (CD-1)	Intramuscular	Females: 13 days before mating to Day 15 of gestation (3 times [a])	0 [b], 70 [c]	Maternal animals 70 [d]: None Embryos/fetuses 70 [d]: None F1 offspring 70 [d]: None	Maternal animals (general toxicity, fertility): 70 Embryos/fetuses: 70 F1 offspring: 70	4.2.3.5.2.2

a) Administered at 35 μL/site in the left and right quadriceps muscles 13 days before mating and on Days 6 and 15 of gestation
b) Aqueous solution containing 10 mM histidine, 7.5% [v/w] sucrose, 35 mM sodium chloride, 1 mM magnesium chloride, 0.1% polysorbate 80, 0.1 mM EDTA, and 0.5% [v/w] ethanol (pH 6.6)
c) Vaxzevria (3.71×10^{10} vp/70 μL)
d) Antibody production against the S-protein was confirmed in maternal animals 14 days after the start of study, 7, 15, and 17.5 days (at the time of cesarean section) after mating, and 7 and 21 days after delivery; in fetuses on Day 17.5 of gestation (at the time of cesarean section); and in F1 offspring 21 days after delivery.+

5.6 Local Tolerance

The local irritation of Vaxzevria was assessed based on the results of the repeat-dose intramuscular toxicity study in mice (CTD 4.2.3.2.1). Reversible mild inflammation was observed at the administration site of Vaxzevria.

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA concluded that there are no particular problems with the toxicity of Vaxzevria.

5.R.1 Effects on germ cells

PMDA asked the applicant to explain the risk of integration into germ cell chromosomes following administration of Vaxzevria.

The applicant's explanation:

In general, an adenovirus vector does not have the capacity of being integrated into host cell chromosomes (integration mechanism) and is therefore considered to be an unintegrated vector (*Nature.* 1997; 389: 239-42). However, in *in vitro* and *in vivo* studies using a high-dose adenoviral vector, although at a low frequency (1×10^{-3} to 1×10^{-6} vp/cell), integration of adenoviral vector DNA into chromosomes has been reported in transformed cell lines, primary cultured cells, liver, etc. (*J Virol.* 1999;73:6141-6, *Proc Nat Acad Sci USA.* 2005;102:13628-33, *J Gene Med.* 2008;10:1176-89, *J Virol.* 2005;79:10999-1013). However, the following

findings regarding germ cells have been reported:

- Adenoviral vectors do not infect sperm cells *(Exp Cell Res.* 2006; 312: 817-30).
- Adenoviral vectors infect spermatogonia but are not integrated into chromosomes (*Proc Nat Acad Sci USA.* 2007; 104: 2596-601).
- Even when adenoviral vectors are administered in the testis, vector DNA are not transmitted to the offspring (*Fertil Steril.* 2008;89:1448-54).
- Even when administered in the uterine artery, adenoviral vectors do not infect oocytes (*Gene Ther.* 2003;10:580-4).

In a biodistribution study using quantitative PCR (lower quantitation limit: 50 copies/reaction) (see Section 4.1), the distribution of DNA fragments derived from Vaxzevria was less than the quantitation limit in the male and female reproductive organs (testis and ovary) following intramuscular administration of Vaxzevria (3.7×10^{10} vp/mouse), and the ratio of Vaxzevria to infectious viral particles was approximately 300 vp/ifu. [12)] These findings suggests that Vaxzevria, administered intramuscularly, is extremely unlikely to be distributed in the reproductive organs and infect germ cells. Based on the above, the applicant considers that there is no risk of integration into germs cell chromosomes following administration of Vaxzevria.

PMDA accepted the applicant's explanation.

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

6.1 Biopharmaceutic Studies and Associated Analytical Methods

In the evaluation of participants' serum response at baseline, anti-nucleoprotein antibodies in the serum were measured by immunoassay using electrochemiluminescence. In the evaluation of humoral immunity, anti-S protein antibodies in sera from participants were measured by the multiplex electrochemiluminescence method, and neutralizing antibodies were measured by a neutralization assay using the pseudovirus or live virus of SARS-CoV-2 (Victoria/1/2020 strain). In the assessment of cellular immunity, peripheral blood mononuclear cells were isolated from the blood of participants, and Th1 cytokines (IFN-γ, IL-2, and TNF-α) and Th2 cytokines (IL-4 and IL-13) were measured by the intracellular cytokine staining and IFN-γ was measured by ELISpot assay. Virological confirmatory testing for COVID-19 was performed using the RT-PCR or the TMA method.

6.2 Clinical Pharmacology Studies

No clinical pharmacology studies have been conducted for the present application.

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

The applicant submitted the efficacy and safety evaluation data: the results of pooled analysis from 1 Japanese study and 4 foreign studies (Table 15). The outline of studies included in the pooled analysis is shown in Table 28 in Section 7.R.1.1.

12) The amount of viral particles in Vaxzevria used for clinical studies was 4.0 to 6.0×10^{10} vp/dose and the number of virus genome copies was 2.9 to 4.7×10^{10} copies/dose (CTD 5.3.4.4.1).

Table 15 Outline of Clinical Studies (Evaluation Data)

Region (Country)	Study identifier	Phase	Population	Participants randomized [a)]	Dosing regimen	Objectives
Japan	D8111C00002	I/II	Healthy participants ≥18 years old	Vaxzevria: 192 Placebo: 64	Two intramuscular doses of Vaxzevria (5×10^{10} vp) or saline at a 4-week interval	Safety, tolerability, immunogenicity
Foreign	Pooled analysis of Studies COV001, COV002, COV003, COV005	-	≥18 years old	Vaxzevria single dose: 1834 Vaxzevria 2 doses: 11977 Meningococcal vaccine single dose: 1762 Meningococcal vaccine 2 doses or meningococcal vaccine + placebo: 10200	See Sections 7.1.2, 7.1.3, 7.2.1, and 7.3.1.	Efficacy, safety, immunogenicity

Meningococcal vaccine: quadrivalent meningococcal conjugate vaccine

a) The number of vaccinated participants is shown for the pooled analysis of foreign studies.

Formulations and dose levels of Vaxzevria used in these studies are shown in Table 55 in Section 11.1. Study participants in the dosing groups to be included in the pooled analysis were randomized to receive a single dose or 2 doses of either Vaxzevria (2 to 5×10^{10} vp) or a control vaccine (meningococcal vaccine or saline). In the pooled analysis, Vaxzevria 5×10^{10} vp or equivalent was handled as a standard dose (SD), and Vaxzevria 2×10^{10} vp, 2.2×10^{10} vp, or 2.5×10^{10} vp were handled as a low dose (LD).

7.1 Phase I/II Studies

7.1.1 Japanese Phase I/II Study (CTD 5.3.5.1.1: Study D8111C00002; ongoing since August 2020; data lock points: [redacted], 20[redacted] [primary analysis] and [redacted], 20[redacted] [additional analysis])

A randomized, double-blind, placebo-controlled, parallel-group study is ongoing at 5 sites in Japan, to investigate the safety, tolerability, and immunogenicity of Vaxzevria in Japanese healthy participants aged ≥18 years (planned sample size, 256 participants [192 in the Vaxzevria group and 64 in the placebo group]). In all participants, data were cut off at the time of completing the visit at 56 days after first dose.

The dosing regimen was 2 intramuscular doses of the study vaccine (Vaxzevria 5×10^{10} vp or saline) administered at a 4-week interval (window for the second dose is ± 2 days). This study has 2 age cohorts (Cohort C, 18 to 55 years old; Cohort D, ≥56 years old), and Cohort D consists of 2 subcohorts (Subcohort D1, 56 to 69 years old; Subcohort D2, ≥70 years old). Participants were randomized to the Vaxzevria or placebo group at a ratio of 3:1. In Cohort D, age (D1 or D2) was considered as a randomization stratification factor.

All 256 randomized participants received ≥1 dose of the study vaccine and were included in the Total Vaccinated Analysis Set (TVS), which was used as the safety analysis population. The following are a breakdown of all participants:

Cohort C: 128 in total (96 in the Vaxzevria group; 32 in the placebo group)

Cohort D: 128 in total (96 in the Vaxzevria group; 32 in the placebo group, [Subcohort D1, 86 in total (65 in the Vaxzevria group; 21 in the placebo group); Subcohort D2, 42 in total (31 in the Vaxzevria group; 11 in the placebo group)])

Of these participants, the following participants were included in the Fully Vaccinated Analysis Set-1 (FVS-1), which was used for the primary analysis of the immunogenicity endpoints: 61 participants in the Vaxzevria group (27 in Cohort C and 34 in Cohort D [22 in Subcohort D1 and 12 in Subcohort D2]) and 20 participants in

the placebo group (9 in Cohort C and 11 in Cohort D [8 in Subcohort D1 and 3 in Subcohort D2]). These participants had been enrolled before a temporary interruption of the study (explained below), received 2 doses of the study vaccine, had no major protocol deviation, and had no seroresponse against SARS-CoV-2 nucleocapsid antigen (≥4-fold rise in antibody titers from baseline) until 56 days after the first dose. The following participants did not receive the second dose: 14 in Cohort C (12 in the Vaxzevria group vs. 2 in the placebo group [the same order applies hereinafter], including 12 who discontinued the study after the study was restarted following a temporary interruption), 5 in Subcohort D1 (4 vs. 1, all of them discontinued the study after the study was restarted following a temporary interruption), and 0 in Subcohort D2. The reason for not receiving the second dose was participants' requests in all of them.

The original protocol stated that the primary analysis would include the immunogenicity data of all participants up to 56 days after the first dose (protocol version [redacted], dated [redacted], 20[redacted]). However, all studies of Vaxzevria were temporarily interrupted following a temporary interruption of Study COV002 (which is ongoing in UK, sponsored by the University of Oxford) to evaluate safety data on a serious adverse event reported in the study (See Section 7.2.1). Japanese Study D8111C00002 was also temporarily interrupted from September 7 to 30, 2020. At the start of the temporary interruption (September 7, 2020), 99 participants had been vaccinated. The protocol was revised to amend the analysis plan in order to avoid delays in evaluation and application for approval of Vaxzevria in Japan (protocol version [redacted], dated [redacted], 20[redacted]). The amended analysis plan uses FVS-1 in the primary analysis. The Fully Vaccinated Analysis Set-2 (FVS-2) used for additional analyses of immunogenicity endpoints included 174 participants in the Vaxzevria group (83 in Cohort C and 91 in Cohort D [61 in Subcohort D1 and 30 in Subcohort D2]) and 60 participants in the placebo group (29 in Cohort C and 31 in Cohort D [20 in Subcohort D1 and 11 in Subcohort D2]) who received 2 doses of the study vaccine without important protocol deviation.

The rate of specific IgG antibody response to SARS-CoV-2 S protein (i.e., proportion of participants with a ≥4-fold rise in antibody titers from baseline) at 28 days after the second dose (primary endpoint), was 100% in all participants receiving Vaxzevria and 0% in all participants receiving placebo in Cohorts C and D who were included in FVS-1 and FVS-2.

The following is the rate of neutralizing antibody response to SARS-CoV-2 measured by neutralization assay with pseudovirus (i.e., proportion of participants with a ≥4-fold rise in antibody titers from baseline) at 28 days after the second dose [2-sided 95% CI: Clopper-Pearson method]:

FVS-1

Cohort C: 63.0% (17 of 27 participants) [42.4, 80.6] in the Vaxzevria group and 0% (0 of 9 participants) [0.0, 33.6] in the placebo group.

Cohort D: 68.8% (22 of 32 participants) [50.0, 83.9] in the Vaxzevria group and 0% (0 of 11 participants) [0.0, 28.5] in the placebo group.

FVS-2

Cohort C: 67.5% (54 of 80 participants) [56.1, 77.6] in the Vaxzevria group and 0% (0 of 29 participants) [0.0, 11.9] in the placebo group.

Cohort D: 57.0% (49 of 86 participants) [45.8, 67.6] in the Vaxzevria group and 0% (0 of 31 participants) [0.0, 11.6] in the placebo group.

Changes in neutralizing antibody titers in FVS-1 and FVS-2 are shown in Table 16.

Table 16 Changes in Neutralizing Antibody Titers to SARS-CoV-2 by Cohort (by Neutralization Assay with Pseudovirus, FVS)

Timepoint		Vaxzevria					Placebo
		Cohort C	Cohort D	Subcohort D1	Subcohort D2	All	All
FVS-1 (primary analysis)							
Baseline	N	27	34	22	12	61	20
	GMT	**20.0**	**20.0**	**20.0**	**20.0**	**20.0**	**20.0**
	[2-sided 95% CI]	-	-	-	-	-	-
28 days after first dose	N	25	33	21	12	58	20
	GMT	**77.0**	**67.1**	**69.0**	**63.7**	**71.2**	**20.0**
	[2-sided 95% CI]	[48.9, 121.2]	[44.8, 100.4]	[40.6, 117.6]	[31.1, 130.6]	[53.1, 95.4]	-
28 days after second dose	N	27	32	21	11	59	20
	GMT	**83.7**	**122.8**	**123.0**	**122.2**	**103.0**	**20.0**
	[2-sided 95% CI]	[57.9, 120.9]	[83.3, 180.9]	[73.7, 205.4]	[61.3, 243.4]	[78.9, 134.4]	-
FVS-2 (additional analysis)							
Baseline	N	83	91	61	30	174	60
	GMT	**20.8**	**20.0**	**20.0**	**20.0**	**20.4**	**20.4**
	[2-sided 95% CI]	[19.2, 22.6]	-	-	-	[19.6, 21.2]	[19.6, 21.3]
28 days after first dose	N	75	85	56	29	160	58
	GMT	**67.3**	**46.1**	**44.6**	**49.1**	**55.0**	**20.6**
	[2-sided 95% CI]	[50.7, 89.2]	[36.6, 58.1]	[33.3, 59.8]	[32.9, 73.3]	[45.9, 66.0]	[19.5, 21.7]
28 days after second dose	N	80	86	58	28	166	59
	GMT	**107.3**	**90.0**	**101.5**	**70.2**	**98.0**	**20.0**
	[2-sided 95% CI]	[84.2, 136.7]	[70.1, 115.6]	[74.3, 138.5]	[45.6, 108.1]	[82.4, 116.5]	-

The follow-up period for safety was determined as follows:

- Solicited AEs (adverse reactions) (local [injection site pain; erythema/redness; tenderness; swelling; and induration] and systemic [pyrexia; chills; myalgia; fatigue; headache; malaise, nausea; and vomiting]): for 7 days following the first and second doses of the study vaccine (collected by participant diary)
- Unsolicited AEs: from the first dose through 28 days after the last dose of the study vaccine
- Serious adverse events and adverse events of special interest: from the first dose through 12 months after the last dose of the study vaccine
- Change from baseline in the laboratory values: for 28 days after the last dose (at Days 7, 28, 35, and 56 after the first dose)

The planned follow-up period of solicited AEs was 7 days after vaccination (8 days in total). Actually, however, solicited AEs collected by Day 6 after vaccination (7 days in total) were evaluated because there was an error in the participant diary form.

Table 17 shows solicited AEs occurring by Day 6 after each vaccination in TVS. Tables 18-1 and 18-2 show unsolicited AEs occurring in ≥2 participants during the 28 days after the first or second dose and such AEs for which a causal relationship with the study vaccine could not be ruled out.

Table 17 Solicited AEs occurring during the 6 days after the first or second dose (TVS)

	Cohort C		Cohort D		Subcohort D1		Subcohort D2		All	
	Vaxzevria n (%)	Placebo n (%)	Vaxzevria n (%)	Placebo n (%)	Vaxzevria n (%)	Placebo n (%)	Vaxzevria n (%)	Placebo n (%)	Vaxzevria n (%)	Placebo n (%)
Local (after the first dose)										
	(N = 96)	(N = 32)	(N = 96)	(N = 32)	(N = 65)	(N = 21)	(N = 31)	(N = 11)	(N = 192)	(N = 64)
Injection site pain	64 (66.7)	3 (9.4)	36 (37.5)	1 (3.1)	30 (46.2)	1 (4.8)	6 (19.4)	0	100 (52.1)	4 (6.3)
Erythema/redness	0	0	1 (1.0)	1 (3.1)	1 (1.5)	1 (4.8)	0	0	1 (0.5)	1 (1.6)
Tenderness	52 (54.2)	2 (6.3)	33 (34.4)	1 (3.1)	26 (40.4)	1 (4.8)	7 (22.6)	0	85 (44.3)	3 (4.7)
Swelling	1 (1.0)	0	0	0	0	0	0	0	1 (0.5)	0
Induration	3 (3.1)	0	1 (1.0)	0	1 (1.5)	0	0	0	4 (2.1)	0
Local (after the second dose)										
	(N = 84)	(N = 30)	(N = 92)	(N = 31)	(N = 61)	(N = 20)	(N = 31)	(N = 11)	(N = 176)	(N = 61)
Injection site pain	22 (26.2)	2 (6.7)	19 (20.7)	0	13 (21.3)	0	6 (19.4)	0	41 (23.3)	2 (3.3)
Erythema/redness	1 (1.2)	0	0	0	0	0	0	0	1 (0.6)	0
Tenderness	30 (35.7)	2 (6.7)	30 (32.6)	0	25 (41.0)	0	5 (16.1)	0	60 (34.1)	2 (3.3)
Swelling	0	0	1 (1.1)	0	0	0	1 (3.2)	0	1 (0.6)	0
Induration	1 (1.2)	0	2 (2.2)	0	1 (1.6)	0	1 (3.2)	0	3 (1.7)	0
Systemic (after the first dose)										
	(N = 96)	(N = 32)	(N = 96)	(N = 32)	(N = 65)	(N = 21)	(N = 31)	(N = 11)	(N = 192)	(N = 64)
Pyrexia	15 (15.6)	0	4 (4.2)	0	3 (4.6)	0	1 (3.2)	0	19 (9.9)	0
Chills	25 (26.0)	0	13 (13.5)	0	10 (15.4)	0	3 (9.7)	0	38 (19.8)	0
Myalgia	42 (43.8)	3 (9.4)	26 (27.1)	0	23 (35.4)	0	3 (9.7)	0	68 (35.4)	3 (4.7)
Fatigue	37 (38.5)	4 (12.5)	17 (17.7)	2 (6.3)	13 (20.0)	0	4 (12.9)	2 (18.2)	54 (28.1)	6 (9.4)
Headache	33 (34.4)	2 (6.3)	15 (15.6)	0	14 (21.5)	0	1 (3.2)	0	48 (25.0)	2 (3.1)
Malaise	49 (51.0)	1 (3.1)	18 (18.8)	2 (6.3)	15 (23.1)	1 (4.8)	3 (9.7)	1 (9.1)	67 (34.9)	3 (4.7)
Nausea	5 (5.2)	0	4 (4.2)	0	2 (3.1)	0	2 (6.5)	0	9 (4.7)	0
Vomiting	3 (3.1)	0	0	0	0	0	0	0	3 (1.6)	0
Systemic (after the second dose)										
	(N = 84)	(N = 30)	(N = 92)	(N = 31)	(N = 61)	(N = 20)	(N = 31)	(N = 11)	(N = 176)	(N = 61)
Pyrexia	2 (2.4)	0	1 (1.1)	1 (3.2)	1 (1.6)	0	0	1 (9.1)	3 (1.7)	1 (1.6)
Chills	0	0	1 (1.1)	0	1 (1.6)	0	0	0	1 (0.6)	0
Myalgia	14 (16.7)	3 (10.0)	15 (16.3)	0	13 (21.3)	0	2 (6.5)	0	29 (16.5)	3 (4.9)
Fatigue	13 (15.5)	3 (10.0)	6 (6.5)	0	5 (8.2)	0	1 (3.2)	0	19 (10.8)	3 (4.9)
Headache	14 (16.7)	4 (13.3)	3 (3.3)	1 (3.2)	3 (4.9)	1 (5.0)	0	0	17 (9.7)	5 (8.2)
Malaise	12 (14.3)	2 (6.7)	7 (7.6)	1 (3.2)	5 (8.2)	1 (5.0)	2 (6.5)	0	19 (10.8)	3 (4.9)
Nausea	0	0	2 (2.2)	0	1 (1.6)	0	1 (3.2)	0	2 (1.1)	0
Vomiting	0	0	0	0	0	0	0	0	0	0

N = number of participants analyzed; n = number of participants with events

Table 18-1 Unsolicited AEs occurring in ≥2 participants during the 28 days after the first or second dose (TVS)

Event term PT (MedDRA/J Ver. 23.1)	Cohort C		Cohort D		Subcohort D1		Subcohort D2		All	
	Vaxzevria n (%)	Placebo n (%)	Vaxzevria n (%)	Placebo n (%)	Vaxzevria n (%)	Placebo n (%)	Vaxzevria n (%)	Placebo n (%)	Vaxzevria n (%)	Placebo n (%)
	(N = 96)	(N = 32)	(N = 96)	(N = 32)	(N = 65)	(N = 21)	(N = 31)	(N = 11)	(N = 192)	(N = 64)
Tenderness	8 (8.3)	0	3 (3.1)	0	2 (3.1)	0	1 (3.2)	0	11 (5.7)	0
Injection site pain	8 (8.3)	0	0	0	0	0	0	0	8 (4.2)	0
Myalgia	5 (5.2)	1 (3.1)	1 (1.0)	0	1 (1.5)	0	0	0	6 (3.1)	1 (1.6)
Body temperature increased	5 (5.2)	0	0	0	0	0	0	0	5 (2.6)	0
Fatigue	4 (4.2)	1 (3.1)	0	2 (6.3)	0	0	0	2 (18.2)	4 (2.1)	3 (4.7)
Malaise	3 (3.1)	0	1 (1.0)	1 (3.1)	1 (1.5)	0	0	1 (9.1)	4 (2.1)	1 (1.6)
Back pain	1 (1.0)	0	1 (1.0)	0	0	0	1 (3.2)	0	2 (1.0)	0
Chest pain	2 (2.1)	0	0	0	0	0	0	0	2 (1.0)	0
Constipation	1 (1.0)	0	1 (1.0)	0	0	0	1 (3.2)	0	2 (1.0)	0
Dental caries	1 (1.0)	0	1 (1.0)	0	1 (1.5)	0	0	0	2 (1.0)	0
Diarrhoea	2 (2.1)	0	0	2 (6.3)	0	1 (4.8)	0	1 (9.1)	2 (1.0)	2 (3.1)
Headache	2 (2.1)	1 (3.1)	0	0	0	0	0	0	2 (1.0)	1 (1.6)
Injection site erythema	0	0	2 (2.1)	0	2 (3.1)	0	0	0	2 (1.0)	0
Oropharyngeal pain	1 (1.0)	0	1 (1.0)	0	1 (1.5)	0	0	0	2 (1.0)	0
Pharyngitis	1 (1.0)	0	1 (1.0)	0	1 (1.5)	0	0	0	2 (1.0)	0
Pruritus	0	0	2 (2.1)	0	2 (3.1)	0	0	0	2 (1.0)	0

N = number of participants analyzed; n = number of participants with events

Table 18-2 Unsolicited AEs occurring in ≥2 participants during the 28 days after the first or second dose for which causal relationship with study vaccine could not be ruled out (TVS)

Event term PT (MedDRA/J Ver. 23.1)	Cohort C		Cohort D		Subcohort D1		Subcohort D2		All	
	Vaxzevria n (%)	Placebo n (%)	Vaxzevria n (%)	Placebo n (%)	Vaxzevria n (%)	Placebo n (%)	Vaxzevria n (%)	Placebo n (%)	Vaxzevria n (%)	Placebo n (%)
	(N = 96)	(N = 32)	(N = 96)	(N = 32)	(N = 65)	(N = 21)	(N = 31)	(N = 11)	(N = 192)	(N = 64)
Tenderness	8 (8.3)	0	3 (3.1)	0	2 (3.1)	0	1 (3.2)	0	11 (5.7)	0
Injection site pain	8 (8.3)	0	0	0	0	0	0	0	8 (4.2)	0
Myalgia	5 (5.2)	1 (3.1)	1 (1.0)	0	1 (1.5)	0	0	0	6 (3.1)	1 (1.6)
Fatigue	4 (4.2)	1 (3.1)	0	2 (6.3)	0	0	0	2 (18.2)	4 (2.1)	3 (4.7)
Malaise	3 (3.1)	0	1 (1.0)	1 (3.1)	1 (1.5)	0	0	1 (9.1)	4 (2.1)	1 (1.6)
Body temperature increased	4 (4.2)	0	0	0	0	0	0	0	4 (2.1)	0
Diarrhoea	2 (2.1)	0	0	1 (3.1)	0	1 (4.8)	0	0	2 (1.0)	1 (1.6)
Headache	2 (2.1)	1 (3.1)	0	0	0	0	0	0	2 (1.0)	1 (1.6)
Injection site erythema	0	0	2 (2.1)	0	2 (3.1)	0	0	0	2 (1.0)	0

N = number of participants analyzed; n = number of participants with events

The most common unsolicited AE (incidence of ≥5% in the Vaxzevria or placebo group) was tenderness in 11 participants (5.7%) in the Vaxzevria group. There were no death or adverse events resulting in discontinuation by 28 days after the last dose. A serious adverse event was observed in 1 participant in the placebo group (cervical dysplasia), but the causal relationship with the study vaccine was ruled out.

7.1.2 Foreign Phase I/II Study (CTD 5.3.5.1.2: Study COV001; ongoing since April 2020)

A randomized, single-blind, controlled study is ongoing at 7 sites (as of November 2020) in UK, to evaluate the safety, immunogenicity, and efficacy of vaccination with Vaxzevria or meningococcal vaccine in healthy participants aged 18 to 55 years. Participants were randomized to the Vaxzevria groups or the meningococcal vaccine groups at the ratio of 1:1, excluding Group 3.

The dosing regimen determined in the protocol version [redacted] (dated [redacted], 20[redacted]) was intramuscular administration of a single dose (SD group) or 2 doses (SDSD group) of Vaxzevria 5×10^{10} vp, 1 dose each of Vaxzevria 5×10^{10} vp and 2.5×10^{10} vp (SDLD group), or a single dose or 2 doses of meningococcal vaccine 0.5 mL (see Table 19). The participants in Group 4 were recommended to take 1,000 mg acetaminophen orally every 6 hours for 24 hours after the study vaccination. For the pooled analysis, study data (including the results of this study) were pooled and analyzed based on the dosing regimens shown in Table 19.

Major amendments of the protocol of this study up to the version [redacted] (dated [redacted], 20[redacted]) are shown in Section 11.3.

As for the safety, solicited AEs and unsolicited AEs were planned to be evaluated by collecting participant diaries from all participants in principle. However, participants enrolled in Groups 2f, 2g, 4c, and 4d were not to keep the participant diary after the second dose of the study vaccine.

As of December 2020, 1,067 participants had been randomized, and 1,067 participants received the study vaccine (116 in the SD group; 386 in the SDSD group; 32 in the SDLD group; 121 in the meningococcal vaccine single dose group; and 412 in the meningococcal vaccine 2-dose group).

This study is ongoing as of March 2021. The results of this study were initially planned to be evaluated

independently. However, the pooled analysis was planned to confirm the efficacy of Vaxzevria earlier because the novel coronavirus pandemic was rapidly spreading (see Section 7.R.1.1). In the protocol version [redacted] (dated [redacted], 20[redacted]) and the Statistical Analysis Plan version [redacted] of the pooled analysis (dated [redacted], 20[redacted]), the original plan was changed to add data from this study to the pooled analysis and to conduct an independent analysis of this study at the end of study as the final analysis.

Table 19 Study Vaccine, Planned Number of Participants, and Objectives of Study COV001

Group	Study vaccine, number of doses	Interval between doses (window)	SD/LD [a)]	Planned number of participants	Objective
Group 1	1a) Vaxzevria 5×10^{10} vp, single dose	-	SD	44	Phase I part
	1b) Meningococcal vaccine, single dose	-	-	44	
Group 2	2a) Vaxzevria 5×10^{10} vp, single dose	-	SD	Max 206	Phase II part The groups 2c to 2g were added based on the results of immunogenicity in Group 3 (see Section 11.3).
	2b) Meningococcal vaccine, single dose	-	-	Max 206	
	2c) Vaxzevria 5×10^{10} vp, 2 doses	8 weeks apart (-7 to +14 days)	SDSD	Max 20 from 2a	
	2d) Vaxzevria 5×10^{10} vp + Vaxzevria 2.5×10^{10} vp, 1 dose each	8 weeks apart (-7 to +14 days)	SDLD	Max 32 from 2a	
	2e) Meningococcal vaccine, 2 doses	8 weeks apart (-7 to +14 days)	-	Max 10 from 2b	
	2f) Vaxzevria 5×10^{10} vp + Vaxzevria 3.5 to 6.5×10^{10} vp, 1 dose each	≥4 weeks apart (As early as possible)	SDSD	Max 154 from 2a	
	2g) Meningococcal vaccine, 2 doses	≥4 weeks apart (As early as possible)	-	Max 196 from 2b	
Group 3	a1) Vaxzevria 5×10^{10} vp, 2 doses	4 weeks apart (-7 to +7 days)	SDSD	10	Evaluation of immunogenicity after 2 doses (not-randomized group)
Group 4	4a) Vaxzevria 5×10^{10} vp, single dose	-	SD	Max 290	Phase II part The groups 4c and 4d were added based on the results of immunogenicity in Group 3 (see Section 11.3).
	4b) Meningococcal vaccine, single dose	-	-	Max 290	
	4c) Vaxzevria 5×10^{10} vp + Vaxzevria 3.5 to 6.5×10^{10} vp, 1 dose each	≥4 weeks apart (As early as possible)	SDSD	Max 290 from 4a	
	4d) Meningococcal vaccine, 2 doses	≥4 weeks apart (As early as possible)	-	Max 290 from 4b	

a) SD (Vaxzevria 5×10^{10} vp), LD (Vaxzevria 2.5×10^{10} vp)

7.1.3 Foreign Phase I/II Study (CTD 5.3.5.1.5: Study COV005; ongoing since June 2020)

A randomized, double-blind, placebo-controlled study is ongoing at 10 sites in South Africa (as of September 2020), to evaluate the safety, immunogenicity, and efficacy of administration of Vaxzevria versus placebo in healthy participants or HIV-positive adults 18 to 65 years old. Participants were randomized to the Vaxzevria group or the placebo group at a ratio of 1:1.

The dosing regimen determined in the protocol version [redacted] (dated [redacted], 20[redacted]) was 2 intramuscular doses of Vaxzevria 5×10^{10} vp or saline 0.5 mL at a 4-week interval, as shown in Table 20. For the pooled analysis, study data (including the results of this study) were pooled and analyzed based on the dosing regimens shown in Table 20.

Table 20 Participants, Study Vaccine, Planned Number of Participants, and Objectives of Study COV005

Group	Participants	Study vaccine, number of doses	Interval between doses (window)	SD/LD	Planned number of participants	Objective
Group 1	HIV-negative adults	Vaxzevria 5×10^{10} vp or saline, 2 doses	4 weeks apart (-7 to +7 days)	SDSD	70	Safety, immunogenicity
Group 2a	HIV-negative adults	Vaxzevria 5×10^{10} vp or saline, 2 doses [a)]	4 weeks apart (-7 to +7 days)	SDSD or LDSD	250	Efficacy, safety, and immunogenicity
Group 2b	HIV-negative adults	Vaxzevria 5×10^{10} vp or saline, 2 doses [a)]	4 weeks apart (-7 to +7 days)	SDSD or LDSD	1650	Efficacy, safety, and immunogenicity
Group 3	HIV-positive adults	Vaxzevria 5×10^{10} vp or saline, 2 doses	4 weeks apart (-7 to +7 days)	SDSD	100 [b)]	Safety, immunogenicity

a) All participants were scheduled to receive Vaxzevria SD. However, some early participants (44 participants; 8 in Group 2a and 36 in Group 2b) were not given SD (5×10^{10} vp) but LD (approximately 2×10^{10} vp) due to an error in quantification of viral particles. Consequently, in the SDSD population in this study, 8 participants in Group 2a and 15 participants in Group 2b received LDSD (see Sections 11.1 and 11.5).
b) The number of participants was changed from 50 to 100 in the protocol version [redacted] (see Section 11.3).

Major amendments of the protocol of this study up to version [redacted] (dated [redacted], 20[redacted]) are shown in Section 11.3.

As for the safety, solicited AEs and unsolicited AEs were planned to be evaluated by collecting participant diaries from all participants.

As of December 2020, 2,026 participants had been randomized, and 2,021 participants received ≥1 dose of the study vaccine (937 in the SDSD group; 21 in the LDSD group; 23 in the SDLD group; 31 in the SD group; 27 in the placebo single dose group; and 982 in the placebo 2-dose group).

This study is ongoing as of March 2021. The results of this study were initially planned to be evaluated independently. However, the pooled analysis was planned to confirm the efficacy of Vaxzevria earlier because the novel coronavirus pandemic was rapidly spreading (see Section 7.R.1.1). In the protocol version [redacted] (dated [redacted], 20[redacted]) and the Statistical Analysis Plan version [redacted] of the pooled analysis (dated [redacted], 20[redacted]), the original plan was changed to add data from this study to the pooled analysis and to conduct an independent analysis of this study at the end of study as the final analysis.

Considering the impact on public health, an unscheduled interim analysis was conducted to evaluate potential impact of SARS-CoV-2 variants on the immunogenicity and efficacy of Vaxzevria (see Section 7.R.2.4). The analysis was conducted by the vaccine team at the University of the Witwatersrand using the cut-off data as of [redacted], 20[redacted]. The independent data safety monitoring committee reviewed the efficacy data and unblinded safety data as of the cut-off time of interim data. All participants and study staff, excluding those who prepare and administer the study vaccine, remain blinded.

7.2 Phase II/III Study

7.2.1 Foreign Phase II/III Study (CTD 5.3.5.1.3: Study COV002; ongoing since May 2020)

A randomized, single-blind, controlled study is ongoing at 21 sites in UK (as of November 2020), to evaluate the efficacy, safety, and immunogenicity of vaccination with Vaxzevria or meningococcal vaccine in healthy participants aged ≥18 years and HIV-positive adults aged 18 to 55 years.

The dosing regimen determined in the protocol version [redacted] (dated [redacted], 20[redacted]) is shown in Table 21. This study consisted of Groups 1 to 12. The participants in Groups 4, 6, 9, and 10 were recommended to take 1,000 mg acetaminophen orally every 4 to 6 hours for 24 hours (total dose up to 4,000 mg) after the study vaccination. For the pooled analysis, study data (including the results of this study) were pooled and analyzed based on the dosing regimens shown in Table 21.

Major amendments of the protocol of this study up to the version [redacted] (dated [redacted], 20[redacted]) are shown in Section 11.3.

As for the safety, solicited AEs and unsolicited AEs were planned to be evaluated by collecting participant diaries from all participants in Groups 1, 2, 3, 5, 7, 8, 11, and 12 and some participants in Groups 4, 6, 9, and 10 (max 1,000 participants each in Groups 4 and 6, and around 500 participants each in Groups 9 and 10). Participants in Groups 1, 2, 3, 5, 7, 8, 11, and 12 were required to report solicited AEs for 7 days after each dose of the study vaccine and unsolicited AEs for 28 days after each dose of the study vaccine. Approximately 3,000 participants in Groups 4, 6, 9, and 10 were required to report both solicited and unsolicited AEs only for 7 days after each dose of the study vaccine.

Table 21 Participants, Study Vaccine, Planned Number of Participants, and Objectives of Study COV002

Group	Participants	Study vaccine, number of doses	Interval between doses (window)	SD/LD	Planned number of participants	Objective
Group 1	Adults 56 to 69 years old	a1) Vaxzevria 5×10^{10} vp (Abs 260) [a], single dose	-	LD	30	Safety and immunogenicity in the population 56 to 69 years old. The participants were initially randomized to receive either 1 or 2 doses of Vaxzevria or comparator (4 groups: Groups 1a1, 1a2, 1b1, or 1b2) at a ratio of 3:1:3:1. Following interim immunogenicity results, participants who had been randomized to receive a single dose were all reallocated to receive a second dose of either Vaxzevria SD or comparator (Group 1a3 or 1a4), depending on their original vaccine allocation (protocol version [redacted]).
		a2) Meningococcal vaccine, single dose	-	-	10	
		a3) Vaxzevria 5×10^{10} vp (Abs 260) [a] + Vaxzevria 3.5 to 6.5×10^{10} vp (Abs 260 corrected) [a], 1 dose each	≥4 weeks apart (As early as possible)	LDSD	Max 30 from a1	
		a4) Meningococcal vaccine, 2 doses	≥4 weeks apart (As early as possible)	-	Max 10 from a2	
		b1) Vaxzevria 5×10^{10} vp (Abs 260) [a] + Vaxzevria 2.2×10^{10} vp (qPCR) [c], 1 dose each	28 days apart (+14 days)	LDLD	30	
		b2) Meningococcal vaccine, 2 doses	28 days apart (+14 days)	-	10	
Group 2	Adults ≥70 years old	a1) Vaxzevria 5×10^{10} vp (Abs 260) [a], single dose	-	LD	50	Safety and immunogenicity in the population ≥70 years old. The participants were initially randomized to receive either 1 or 2 doses of Vaxzevria or comparator (4 groups: Groups 2a1, 2a2, 2b1, or 2b2) at a ratio of 5:1:5:1. Following interim immunogenicity results, participants who had been randomized to receive a single dose were all reallocated to receive a second dose (Groups 2a3 or 2a4) of either Vaxzevria SD or comparator, depending on their original vaccine allocation (protocol version [redacted]).
		a2) Meningococcal vaccine, single dose	-	-	10	
		a3) Vaxzevria 5×10^{10} vp (Abs 260) [a] + Vaxzevria 3.5 to 6.5×10^{10} vp (Abs 260 corrected) [a], 1 dose each	≥4 weeks apart (As early as possible)	LDSD	Max 50 from a1	
		a4) Meningococcal vaccine, 2 doses	≥4 weeks apart (As early as possible)	-	Max 10 from a2	
		b1) Vaxzevria 5×10^{10} vp (Abs 260) [a] + Vaxzevria 2.2×10^{10} vp (qPCR) [c], 1 dose each	28 days apart (+14 days)	LDLD	50	
		b2) Meningococcal vaccine, 2 doses	28 days apart (+14 days)	-	10	
Group 3 [d]	Children 5 to 12 years old	a1) Vaxzevria 2.5×10^{10} vp (qPCR) [c], single dose	-	-	30	Safety and immunogenicity in children. The participants were randomized to the Vaxzevria group or the control group at a ratio of 1:1.
		a2) Meningococcal vaccine, single dose	-	-	30	

Group 4	Adults 18 to 55 years old	a1) Vaxzevria 5×10^{10} vp (Abs 260) [a], single dose	-	LD	Max 1775	Originally intended to evaluate the efficacy of Vaxzevria SD vs comparator in participants ≥18 years old. After discovering that this group had received Vaxzevria LD instead of SD, further enrollment to this group was discontinued and a new SD efficacy group (Group 6) was added (protocol version [redacted]). The participants were randomized to the Vaxzevria group or the control group at a ratio of 1:1.
		a2) Meningococcal vaccine, single dose	-	-	Max 1775	
		b1) Vaxzevria 5×10^{10} vp (Abs 260) [a] + Vaxzevria 2.2×10^{10} vp (qPCR) [c], 1 dose each	28 days apart (+14 days)	LDLD	Max 50 from a1	
		b2) Meningococcal vaccine, 2 doses	28 days apart (+14 days)	-	Max 50 from a2	
		c1) Vaxzevria 5×10^{10} vp (Abs 260) [a] + Vaxzevria 3.5 to 6.5×10^{10} vp (Abs 260 corrected) [a] or 5×10^{10} vp (qPCR) [c], 1 dose each	≥4 weeks apart	LDSD	Max 1725 in a1 (excluding those in b1)	
		c2) Meningococcal vaccine, 2 doses	≥4 weeks apart	-	Max 1725 from a2 (excluding those in b2)	
Group 5	Adults 18 to 55 years old	a1) Vaxzevria 5×10^{10} vp (Abs 260) [a], single dose	-	LD	50	Comparison of safety and immunogenicity between different vaccine products with the same visit schedule used in Group 1 in Study COV001. The participants in Groups 5a, 5b, and 5c were randomized to receive Vaxzevria or comparator at a ratio of 1:1. <u>Group 5a (LD [redacted]):</u> Originally a single dose was planned for Groups 5a1 and 5a2, but in response to interim immunogenicity results, participants in these groups were switched to Group 5a3 or 5a4 and received a second dose of either Vaxzevria SD or comparator (protocol version [redacted]). <u>Groups 5b and 5c (SD [redacted]):</u> Evaluated the dose-corrected vaccine product of [redacted] (single dose only). Blood sampling method for immunogenicity differs between Groups 5b and 5c considering the analytical laboratory capacity to do certain B-cell or T-cell assays (protocol version [redacted]). <u>Group 5d (SD [redacted]):</u> This group was added in protocol version [redacted].
		a2) Meningococcal vaccine, single dose	-	-	50	
		a3) Vaxzevria 5×10^{10} vp (Abs 260) [a] + Vaxzevria 3.5 to 6.5×10^{10} vp (Abs 260 corrected) [b], 1 dose each	≥4 weeks apart (As early as possible)	LDSD	Max 50 from a1	
		a4) Meningococcal vaccine, 2 doses	≥4 weeks apart (As early as possible)	-	Max 50 from a2	
		b1) Vaxzevria 5×10^{10} vp (qPCR) [c], single dose	-	SD	Max 25	
		b2) Meningococcal vaccine, single dose	-	-	Max 25	
		c1) Vaxzevria 5×10^{10} vp (qPCR) [c], single dose	-	SD	Max 25	
		c2) Meningococcal vaccine, single dose	-	-	Max 25	
		d1) Vaxzevria 3.5 to 6.5×10^{10} vp (Abs 260 corrected) [b], 2 doses	28 days apart (+14 days)	SDSD	Max 50	
		d2) Meningococcal vaccine, 2 doses	28 days apart (+14 days)	-	Max 10	
Group 6	Adults 18 to 55 years old	a1) Vaxzevria 5×10^{10} vp (qPCR) [c], single dose	-	SD	Max 3000	Originally intended to evaluate the efficacy of a single dose of Vaxzevria SD in the population ≥18 years old, in place of Group 4 (protocol version [redacted]). To facilitate planned enrollment for all age groups, participants ≥56 years old in Group 6 were switched to either Group 9 or 10, newly established groups. As a result, Group 6 included only participants 18 to 55 years old (protocol version [redacted]). The participants were randomized to the Vaxzevria group or the control group at a ratio of 1:1.
		a2) Meningococcal vaccine, single dose	-	-	Max 3000	
		b1) Vaxzevria 5×10^{10} vp (qPCR) [c] + Vaxzevria 3.5 to 6.5×10^{10} vp (Abs 260 corrected) [b] or 5×10^{10} vp (qPCR) [c], 1 dose each	≥4 weeks apart	SDSD	Max 3000 from a1	
		b2) Meningococcal vaccine, 2 doses	≥4 weeks apart	-	Max 3000 from a2	
Group 7	Adults 56 to 69 years old	a1) Vaxzevria 5×10^{10} vp (qPCR) [c], single dose	-	SD	30	Determine the optimal dosing regimen of Vaxzevria SD in populations 56 to 69 years old (identical to the design of original Group 1). The participants were randomized to receive either 1 or 2 doses of Vaxzevria or comparator (4 groups: Group 7a1, 7a2, 7b1, or 7b2) at a ratio of 3:1:3:1.
		a2) Meningococcal vaccine, single dose	-	-	10	
		b1) Vaxzevria 5×10^{10} vp (qPCR) [c], 2 doses	28 days apart (+14 days)	SDSD	30	
		b2) Meningococcal vaccine, 2 doses	28 days apart (+14 days)	-	10	
Group 8	Adults ≥70	a1) Vaxzevria 5×10^{10} vp (qPCR) [c],	-	SD	50	Determine the optimal dosing regimen

	years old	single dose				of Vaxzevria SD in the population ≥70 years old (identical to the design of original Group 2). The participants were randomized to receive either 1 or 2 doses of Vaxzevria or comparator (4 groups: Group 8a1, 8a2, 8b1, or 8b2) at a ratio of 5:1:5:1.
		a2) Meningococcal vaccine, single dose	-	-	10	
		b1) Vaxzevria 5×10^{10} vp (qPCR) [c] + Vaxzevria 3.5 to 6.5×10^{10} vp (Abs 260 corrected) [b] or 5×10^{10} vp (qPCR) [c], 1 dose each	28 days apart (+14 days)	SDSD	50	
		b2) Meningococcal vaccine, 2 doses	28 days apart (+14 days)	-	10	
Group 9	Adults 56 to 69 years old	a1) Vaxzevria 3.5 to 6.5×10^{10} vp (Abs 260 corrected) [b], 2 doses	28 days apart (+14 days)	SDSD	500	Efficacy in the population 56 to 69 years old. Enrollment commenced following the Data Safety Monitoring Board review of the age in Group 1 and Group 2 (protocol version [redacted]). The participants were randomized to the Vaxzevria group or the control group at a ratio of 1:1.
		a2) Meningococcal vaccine, 2 doses	28 days apart (+14 days)	-	500	
Group 10	Adults ≥70 years old	a1) Vaxzevria 3.5 to 6.5×10^{10} vp (Abs 260 corrected) [b], 2 doses	28 days apart (+14 days)	SDSD	500	Efficacy in the population ≥70 years old. Enrollment commenced following the Data Safety Monitoring Board review of the age in Group 1 and Group 2 (protocol version [redacted]). The participants were randomized to the Vaxzevria group or the control group at a ratio of 1:1.
		a2) Meningococcal vaccine, 2 doses	28 days apart (+14 days)	-	500	
Group 11	Adults 18 to 55 years old who have previously received ChAdOx1 vectored vaccine	a1) Vaxzevria 3.5 to 6.5×10^{10} vp (Abs 260 corrected) [b], 2 doses	28 days apart (+14 days)	SDSD	Max 60	Evaluation of effects of previously received ChAdOx1 vectored vaccine (not-randomized group)
Group 12	HIV-positive adults 18 to 55 years old	a1) Vaxzevria 3.5 to 6.5×10^{10} vp (Abs 260 corrected) [b], 2 doses	28 days apart (+14 days)	SDSD	Max 60	Immunogenicity in HIV-infected individuals (not-randomized group)

a) A batch that contained the excipient polysorbate 80 at a high concentration. Viral particles were quantified by spectrophotometry, in which polysorbate 80 interfered with the absorbance. Because of this, the study vaccine containing less viral particles than planned was administered (see Section 11.5). As a result, the following number of participants received LDSD although they had been scheduled to receive SDSD: 29 in Group 1a3, 25 in Group 2a3, 1,400 in Group 4c1, and 41 in Group 5a3.

b) A batch that contained the excipient polysorbate 80 at a high concentration. When viral particles were quantified by spectrophotometry, the absorbance was corrected considering the interference of polysorbate 80.

c) A batch that contained the excipient polysorbate 80 at a high concentration. Viral particles specified in the protocol were quantified correctly by qPCR.

d) Not enrolled. Group 3 was deleted in the protocol version [redacted] (dated [redacted], 20[redacted]) (see Section 11.3).

As of December 2020, 10,748 participants had been randomized, and 10,740 participants received the study vaccine (272 in the LD group; 127 in the LDLD group; 1,540 in the LDSD group; 525 in the SD group; 3,065 in the SDSD group; 657 in the meningococcal vaccine single dose group; and 4,554 in the meningococcal vaccine 2-dose group).

This study is ongoing as of March 2021. The results of this study were initially planned to be evaluated independently. However, the pooled analysis was planned to confirm the efficacy of Vaxzevria earlier because the novel coronavirus pandemic was rapidly spreading (see Section 7.R.1.1). In the protocol version [redacted] (dated [redacted], 20[redacted]) and the Statistical Analysis Plan version [redacted] of the pooled analysis (dated [redacted] 20[redacted]), the original plan was changed to add data from this study to the pooled analysis. Further, the plan was changed to conduct an independent analysis of this study at the end of study as a final analysis, in which efficacy results were positioned as a supplement to the pooled analysis results.

Considering the impact on public health, an unscheduled interim analysis was conducted to evaluate potential impact of SARS-CoV-2 variants on the immunogenicity and efficacy of Vaxzevria (see Section 7.R.2.4). The preliminary analysis and the follow-up analysis were performed using the data extracted from the database as of [redacted], 20[redacted] and as of [redacted], 20[redacted], respectively, by the team of the University of Oxford (the sponsor) according to the standard procedures of the University of Oxford. In UK, the SARS-CoV-2 vaccination was started in the general population on December 8, 2020. This study had been scheduled to be unblinded when vaccines become available in general population. Therefore, at the interim analysis, most of the participants had been unblinded.

7.3 Phase III Study

7.3.1 Foreign Phase III Study (CTD 5.3.5.1.4: Study COV003; ongoing since June 2020)

A randomized, single-blind, controlled study to investigate effects to prevent symptomatic COVID-19 in adults aged ≥18 years is ongoing at 6 sites in Brazil (as of November 2020). The participants were randomized to the Vaxzevria group or the meningococcal vaccine group at a ratio of 1:1.

The dosing regimen determined in the protocol version [redacted] (dated [redacted], 20[redacted]) was intramuscular administration of 1 or 2 doses of Vaxzevria 5×10^{10} vp, a single dose of meningococcal vaccine, or 1 dose each of meningococcal vaccine and saline 0.5 mL (see Table 22). The participants were recommended to receive 500 to 1,000 mg acetaminophen orally every 6 hours for 24 hours after the study vaccination. For the pooled analysis, study data (including the results of this study) were pooled and analyzed based on the dosing regimens shown in Table 22.

Major amendments of the protocol of this study up to the version [redacted] (dated [redacted], 20[redacted]) are shown in Section 11.3.

As for the safety, solicited AEs and unsolicited AEs were planned to be evaluated by collecting participant diaries from 200 participants randomly selected from all participants.

Table 22 Study Vaccine, Planned Number of Participants, and Objectives of Study COV003

Group	Study vaccine, number of doses	Interval between doses (window)	SD/LD	Planned number of participants	Objective
Group 1a	Vaxzevria 5×10^{10} vp, single dose	-	SD	Max 1600	Efficacy, safety, immunogenicity
Group 1b	Meningococcal vaccine, single dose	-	-	Max 1600	
Group 1c	Vaxzevria 5×10^{10} vp + Vaxzevria 3.5 to 6.5×10^{10} vp, 2 doses [a)]	4 to 12 weeks apart (+14 days)	SDSD	Max 5150 [b)] (max 1600 from 1a)	
Group 1d	Meningococcal vaccine + saline, 1 dose each [a)]	4 to 12 weeks apart (+14 days)	-	Max 5150 [b)] (max 1600 from 1b)	

a) Previously enrolled participants in Groups 1a and 1b were instructed to receive a second dose.
b) All participants enrolled after the protocol version [redacted] (dated [redacted], 20[redacted]) were required to consent to receive 2 doses.

As of December 2020, 10,416 participants had been randomized, and 10,416 participants received the study vaccine (890 in the SD group; 4,317 in the SDSD group; 957 in the meningococcal vaccine single dose group; and 4,252 in the meningococcal vaccine 1 dose + placebo 1 dose group).
This study is ongoing as of March 2021. The results of this study were initially planned to be evaluated

independently. However, the pooled analysis was planned to confirm the efficacy of Vaxzevria earlier because the novel coronavirus pandemic was rapidly spreading (see Section 7.R.1.1). In the protocol version [redacted] (dated [redacted], 20[redacted]) and the Statistical Analysis Plan version [redacted] of the pooled analysis (dated [redacted], 20[redacted]), the original plan was changed to add data from this study to the pooled analysis. Further, the plan was changed to conduct an independent analysis of this study at the end of study as a final analysis, in which efficacy results were positioned as a supplement to the pooled analysis results.

7.4 Pooled Analysis of 4 Foreign Studies (Studies COV001, COV002, COV003, and COV005) (CTD 5.3.5.3.1 and 5.3.5.3.2; data cut-off: November 4, 2020 [DCO1] and December 7, 2020 [DCO2])

The pooled analysis of the efficacy and safety was performed using data from 24,257 participants (12,280 in the Vaxzevria group, 11,977 in the control group) from 4 studies in adults aged ≥18 years in UK, Brazil, and South Africa (Studies COV001, COV002, COV003, and COV005) (see Section 7.R.1.1). The dosing regimens of Vaxzevria in the above 4 studies are shown in Sections 7.1.2, 7.1.3, 7.2.1, and 7.3.1.

The subgroups that may confound interpretation of the results (e.g., participants who were not randomized; participants with prior vaccination with a ChAdOx1 vectored vaccine; HIV-positive adults) were identified in the Statistical Analysis Plan version [redacted] of the pooled analysis (dated [redacted], 20[redacted]) and excluded from the pooled analysis.

At the interim analysis (DCO1) 23,753 participants (12,018 in the Vaxzevria group vs. 11,735 in the control group [the same order applies hereinafter]) had been randomized. At the primary analysis (DCO2), 24,257 participants (12,280 vs. 11,977) had been randomized.

As for the safety, randomized participants who received Vaxzevria SD or the corresponding comparator as the first dose were included in the Dose 1 SD for Safety Analysis Set. Among the participants in the Dose 1 SD for Safety Analysis Set, those who provided participant diaries were evaluated for solicited AEs. Among 20,458 participants (10,317 vs. 10,141) included in the primary safety analysis set at the primary analysis (DCO2), 129 (66 vs. 63) discontinued the study prematurely, mainly due to withdrawal of consent by participants (39 vs. 40).

The primary efficacy analysis set included participants who were seronegative at baseline, received LDSD or SDSD, had no SARS-CoV-2 virologically-confirmed COVID-19 [13)] prior to 15 days after the second dose, and had follow-up data starting ≥15 days after the second dose (SDSD + LDSD Seronegative for Efficacy Analysis Set). All analyses were planned to be performed by the study vaccine actually administered. The immunogenicity analysis set included participants who received the LDSD or SDSD study vaccine and from whom results of all measurement points have been obtained (SDSD + LDSD Immunogenicity Analysis Set). The participants not randomized at a ratio of 1:1 between the Vaxzevria group and the control group were not included in the efficacy analysis. In addition, individual studies that reported <5 COVID-19 events were excluded from the efficacy analysis to avoid instability of the model when adjusting for study effects, in accordance with the provisions of Statistical Analysis Plan version [redacted] of the pooled analysis (dated [redacted], 20[redacted]). Therefore, Studies

13) Confirmed by RT-PCR or other nucleic acid amplification test

COV001 and COV005 were not included in the efficacy analysis in the interim analysis (DCO1), but all 4 studies were included in the efficacy analysis in the primary analysis (DCO2).

The number of participants in each analysis set is shown in Table 23, and disposition of participants included in the efficacy analysis set in the interim analysis (DCO1) which was positioned as the confirmatory results of efficacy is shown in Figure 1.

Table 23 Number of Participants in Each Analysis Set

Analysis set	Dosing regimen	Number of participants at the interim analysis (DCO1) (Studies COV001/COV002/COV003/COV005)			Number of participants at the primary analysis (DCO2) (Studies COV001/COV002/COV003/COV005)		
		Vaxzevria	Control	Total	Vaxzevria	Control	Total
Full Analysis Set (randomized population)		12018 (533/5479/ 4999/1007)	11735 (534/5192/ 5003/1006)	23753 (1067/10671/ 10002/ 2013)	12280 (533/5528/ 5206/1013)	11977 (534/5220/ 5210/1013)	24257 (1067/10748/ 10416/2026)
Dose 1 SD for Safety Analysis Set	SDSD SD single dose SDLD	10069 (534/3551/ 4998/ 986)	9902 (533/3384/ 5002/983)	19971 (1067/6935/ 10000/1969)	10317 (534/3588/ 5205/ 990)	10141 (533/3411/ 5209/ 988)	20458 (1067/6999/ 10414/1978)
Participants assessed for solicited AEs in Dose 1 SD for Safety Analysis Set	SDSD SD single dose SDLD	2648 (534/1102/ 100/ 912)	2497 (531/966/ 99/ 901)	5145 (1065/2068/ 199/1813)	2725 (534/1128/ 100/ 963)	2573 (531/983/ 100/959)	5298 (1065/2111/ 200/1922)
SDSD + LDSD Seronegative for Efficacy Analysis Set	SDSD LDSD	5807 (0/3744/ 2063/0)	5829 (0/3804/ 2025/0)	11636 (0/7548/ 4088/0)	8597 (356/4071/ 3414/756)	8581 (385/4136/ 3339/721)	17178 (741/8207/ 6753/1477)
SDSD + LDSD Immunogenicity Analysis Set	SDSD LDSD	1664 (122/1011/ 405/126)	1207 (70/619/ 391/127)	2871 (192/1,630/ 796/253)	2135 (129/1370/ 510/126)	1577 (70/883/ 496/128)	3712 (199/2253/ 1006/254)

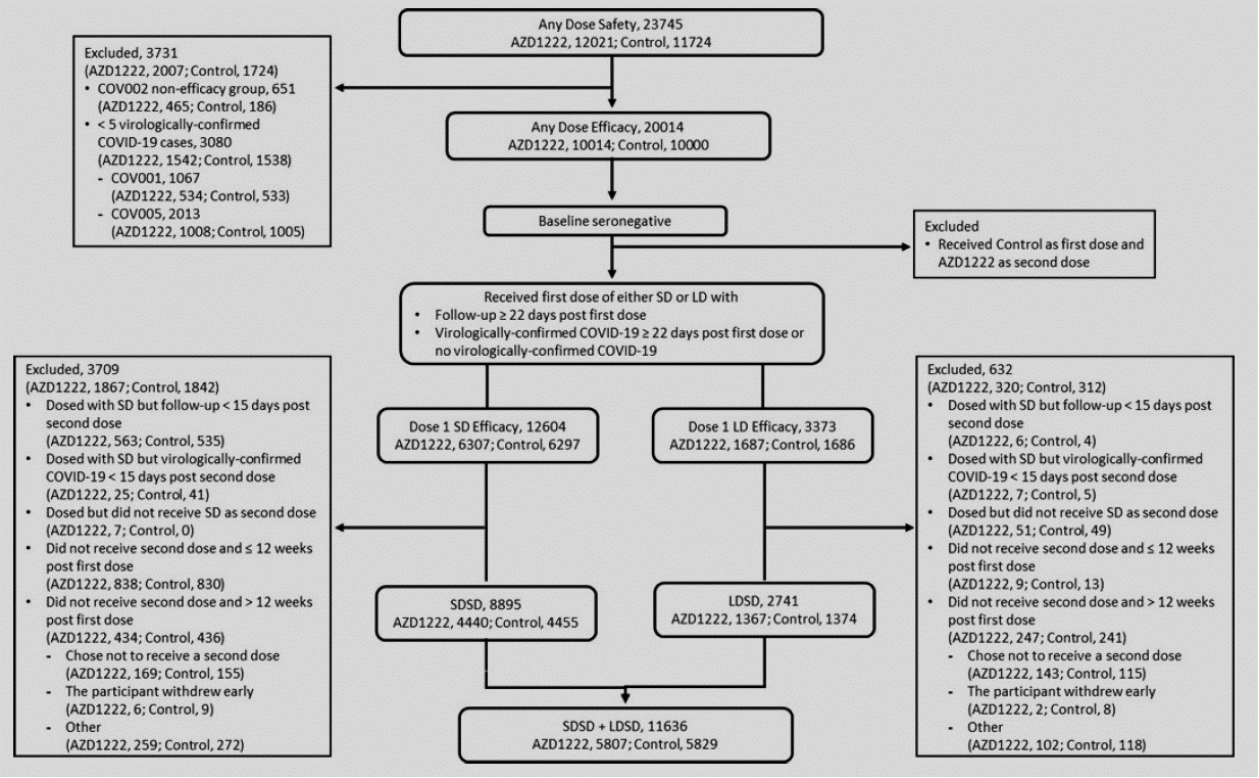


Figure 1 Disposition of Participants Included in the Efficacy Analysis Set in the Interim Analysis of Pooled Analysis (DCO1)
AZD1222, Vaxzevria group; Control, Control group; Any Dose Safety, Any Dose for Safety Analysis Set; Any Dose Efficacy, Any Dose for Efficacy Analysis Set; Baseline seronegative, participants who are seronegative at baseline; Virologically-confirmed COVID-19, Virologically-confirmed COVID-19; Dose 1 SD Efficacy, Dose 1 SD Seronegative for Efficacy Analysis Set; Dose 1 LD Efficacy, Dose 1 LD Seronegative for Efficacy Analysis Set; SDSD, SDSD Seronegative for Efficacy Analysis Set; LDSD, LDSD Seronegative for Efficacy Analysis Set

In the Statistical Analysis Plan version [redacted] of the pooled analysis (dated [redacted], 20[redacted]), the primary efficacy endpoint was VE (VE [%] = 100 × [1- incidence of COVID-19 events in the Vaxzevria group / incidence of COVID-19 events in the control group]) based on "the first case of SARS-CoV-2 virologically confirmed symptomatic COVID-19 occurring ≥15 days after the second dose of study vaccine with ≥1 of the following symptoms: pyrexia of ≥37.8°C, cough, shortness of breath, anosmia, and ageusia." Cases were counted as events only if both (a) the sampling date of positive RT-PCR test or other nucleic acid amplification test and (d) the onset date of COVID-19 symptom(s), were ≥15 days post second dose. In all 4 studies included in the pooled analysis, a blinded, independent endpoint adjudication committee assessed COVID-19 events in all participants with SARS-CoV-2 virologically confirmed results. In the VE analysis, a 20% threshold was determined because this was greatly higher than 0%, and VE was to be assessed by comparing the threshold with the lower limit of the CI.

The first interim analysis was planned to be conducted when 53 COVID-19 events (the primary efficacy endpoint) were observed in participants receiving SDSD of Vaxzevria or the comparator, to allow for prompt decision in the public health emergency in the COVID-19 pandemic. The power was to be 77% assuming that VE is 70% and using the 2-sided significance level of 1.13% and the 20% threshold. It was planned to continue each study and conduct the primary analysis even when the efficacy of Vaxzevria is demonstrated by the interim analysis, in order to conduct further follow-up and collect more cases to estimate preventive effect and duration of efficacy of Vaxzevria in subgroups such as elderly people. The primary analysis was planned to be conducted when 105 COVID-19 events were observed in participants receiving SDSD of Vaxzevria or the comparator. The power was to be 90% assuming that VE is 60%, and using the 2-sided significance level of 4.44% and the 20% threshold. A gamma alpha-spending function was used to control type 1 error for the interim analysis, and the 2-sided significance level was 1.13% at the interim analysis and 4.44% at the primary analysis. However, because cases were accrued rapidly before the data cut-off for the interim analysis (DCO1), 98 COVID-19 events were included in the interim analysis (DCO1) in the SDSD participants (131 COVID-19 events in SDSD + LDSD participants), and the 2-sided significance level at the interim analysis (DCO1) was 4.16% calculated from the gamma (-2.5) alpha-spending function.

In the interim analysis (DCO1), the follow-up period (i.e., on and after 15 days post second dose) [14)] (mean ± SD) was 52.1 ± 24.18 days in the Vaxzevria group and 51.3 ± 22.91 days in the control group in the Dose 1 SD for Safety Analysis Set, and 42.9 ± 18.12 days in the Vaxzevria group and 42.9 ± 17.91 days in the control group in the SDSD + LDSD Seronegative for Efficacy Analysis Set. In the primary analysis (DCO2), the follow-up period (i.e., on and after 15 days post second dose) (mean ± SD) was 68.9 ± 35.75 days in the Vaxzevria group and 68.2 ± 34.87 days in the control group in the Dose 1 SD for Safety Analysis Set, and 64.1 ± 29.86 days in the Vaxzevria group and 64.0 ± 29.49 days in the control group in the SDSD + LDSD Seronegative for Efficacy Analysis Set.

14) The follow-up period was calculated as (last day of at-risk - [the date of second dose + 15 days]) + 1 (day). The last day of at-risk is determined as follows: the onset date of the first event in participants diagnosed with SARS-CoV-2 virologically confirmed COVID-19, the date of completion/discontinuation of study in participants who completed or discontinued the study without event, and the data cut-off date of the analysis in participants continuing the study without event.

As for the efficacy, Table 24 and Figure 2 show the results of the interim analysis (DCO1) of COVID-19 events (primary endpoint) and the cumulative incidence in SDSD + LDSD Seronegative for Efficacy Analysis Set (primary analysis set). The lower limit of the 2-sided 95.84% CI of VE was higher than the predetermined 20% threshold.

Table 24 Vaccine Efficacy against COVID-19 Events Occurring ≥15 Days after the Second Dose of Study Vaccine (Interim Analysis Results) (SDSD + LDSD Seronegative for Efficacy Analysis Set, DCO1)

	Vaxzevria	Control
Number of participants	5807	5829
Number of COVID-19 events (%)	30 (0.52)	101 (1.73)
VE (%) [2-sided 95.84% CI] *1	70.42 [54.84, 80.63]	

*1: Poisson regression model including the study identifier, vaccine group, age group at screening (18 to 55, 56 to 69, and ≥70 years) as factors, as well as the log of the follow-up period as an offset (significance level: 2-sided 0.0416).

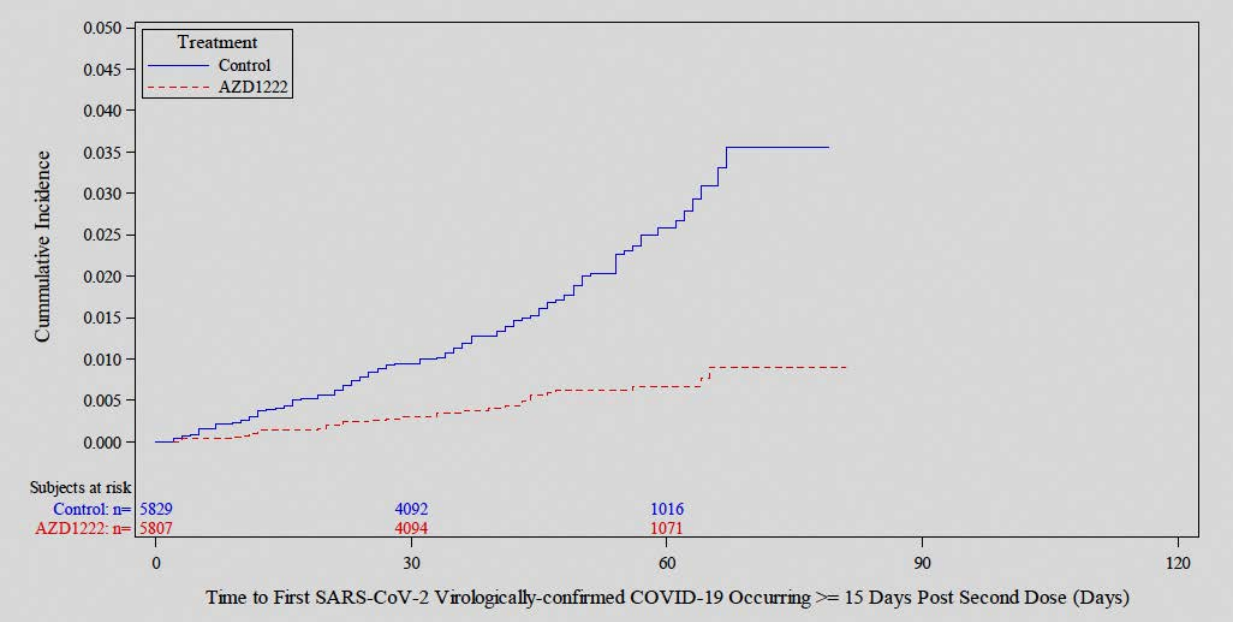


Figure 2 Cumulative Incidence of COVID-19 Events at Interim Analysis (DCO1) (SDSD + LDSD Seronegative for Efficacy Analysis Set)

In the SDSD + LDSD Seronegative for Efficacy Analysis Set (primary analysis set), the results of the primary analysis (DCO2) of COVID-19 events (primary endpoint) and the cumulative incidence are shown in Table 25 and Figure 3. In UK, the SARS-CoV-2 vaccination was started in the general population on December 8, 2020. As Studies COV001 and COV002 had been scheduled to be unblinded when vaccines become available in general population, the date of DCO2 was determined to be December 7, 2020 to ensure that the study results are not affected by the unblinding. The primary analysis (DCO2) was to be conducted when ≥105 COVID-19 events have occurred in participants receiving SDSD of Vaxzevria or the comparator. Actually, however, the primary analysis (DCO2) included 332 COVID-19 events (271 of them were in participants who received SDSD) because of a rapid increase in infected participants and earlier accrual of participants who developed the event before the data cut-off.

Table 25 Vaccine Efficacy against COVID-19 Events Occurring ≥15 Days after the Second Dose (Primary Analysis Results) (SDSD + LDSD Seronegative for Efficacy Analysis Set, DCO2)

	Vaxzevria	Control
Number of participants	8597	8581
Number of COVID-19 events (%)	84 (0.98)	248 (2.89)
VE (%) [2-sided 95% CI] [a)]	66.73 [57.41, 74.01]	

a) Poisson regression model including study identifier, vaccine group, age group at screening (18 to 55, 56 to 69, and ≥70 years) as factors, as well as the log of the follow-up period as an offset.

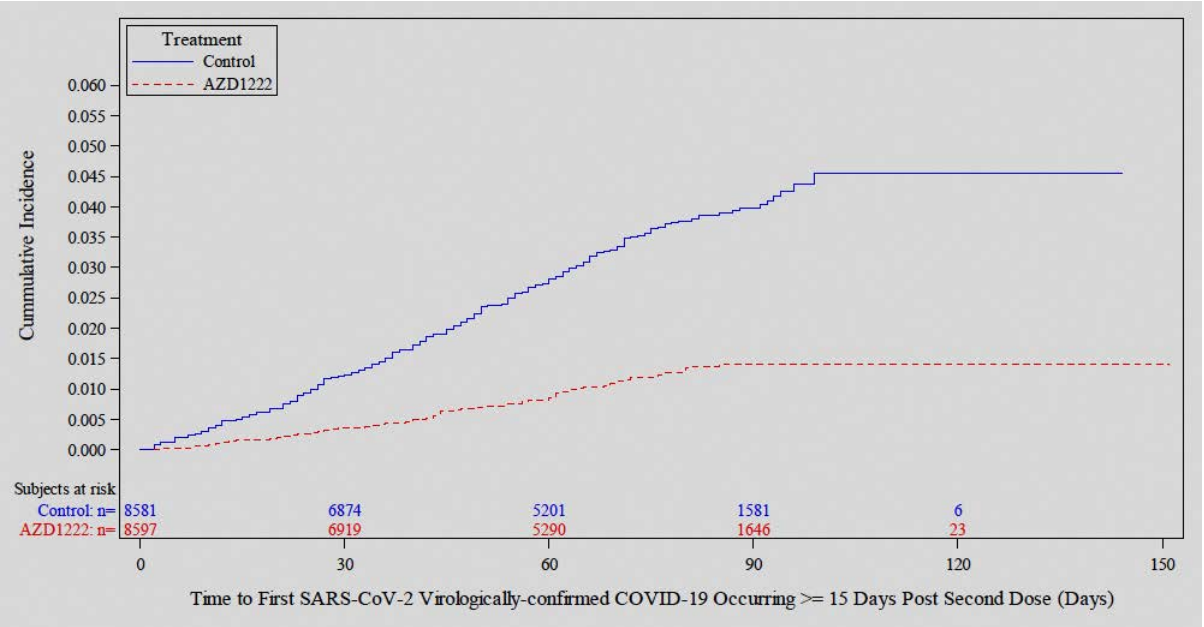


Figure 3 Cumulative Incidence of COVID-19 Events at Primary Analysis (DCO2) (SDSD + LDSD Seronegative for Efficacy Analysis Set)

The follow-up period for safety was determined as follows:

- Solicited AEs (local [injection site pain; tenderness; redness; feeling hot; itching; swelling; and induration] and systemic [pyrexia; feverishness; chills; joint pain; myalgia; fatigue; headache; malaise, nausea; and vomiting]): for 7 days after each dose of the study vaccine (collected by the participant diary)
- Unsolicited AEs: for 28 days after each dose of the study vaccine
- Serious adverse events and adverse events of special interest: from the first dose to 12 months after the last dose of the study vaccine

The planned follow-up period of solicited AEs in Study COV005 was 7 days following vaccination (8 days in total). However, solicited AEs were evaluated for 6 days following vaccination (7 days in total) because there was an error in the participant diary form.

Table 26 show solicited AEs occurring within 7 days following each vaccination in participants assessed for solicited AEs in the Dose 1 SD for Safety Analysis Set (DCO2) (participants included in Dose 1 SD for solicited AE assessment).

Table 26 Solicited AEs occurring within 7 Days Following the First and Second Doses [a)]
(Participants Included in Dose 1 SD for Solicited AE Assessment, DCO2)

Event term	Dose #	Vaxzevria	Control			
			All controls combined	Meningococcal vaccine 2-dose	Meningococcal vaccine + placebo	Placebo 2-dose
		n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Local						
Injection site pain [a)]	First	893/1745 (51.2)	521/1593 (32.7)	467/1493 (31.3)	54/100 (54.0)	-
	Second	273/1011 (27.0)	190/895 (21.2)	179/825 (21.7)	11/70 (15.7)	-
Tenderness	First	1587/2655 (59.8)	892/2496 (35.7)	748/1493 (50.1)	30/100 (30.0)	114/903 (12.6)
	Second	732/1920 (38.1)	411/1794 (22.9)	331/825 (40.1)	6/70 (8.6)	74/899 (8.2)
Redness	First	63/2623 (2.4)	30/2466 (1.2)	24/1493 (1.6)	2/100 (2.0)	4/873 (0.5)
	Second	23/1877 (1.2)	6/1744 (0.3)	5/825 (0.6)	0/70 (0)	1/849 (0.1)
Feeling hot [a)]	First	274/1745 (15.7)	207/1593 (13.0)	197/1493 (13.2)	10/100 (10.0)	-
	Second	78/1011 (7.7)	75/895 (8.4)	74/825 (9.0)	1/70 (1.4)	-
Itching	First	278/2655 (10.5)	150/2495 (6.0)	69/1493 (4.6)	3/100 (3.0)	78/902 (8.6)
	Second	161/1920 (8.4)	78/1794 (4.3)	23/825 (2.8)	0/70 (0)	55/899 (6.1)
Swelling	First	73/2622 (2.8)	34/2466 (1.4)	27/1493 (1.8)	3/100 (3.0)	4/873 (0.5)
	Second	27/1876 (1.4)	10/1745 (0.6)	7/825 (0.8)	0/70 (0)	3/850 (0.4)
Induration [a)]	First	45/1745 (2.6)	28/1593 (1.8)	26/1493 (1.7)	2/100 (2.0)	-
	Second	7/1011 (0.7)	12/895 (1.3)	12/825 (1.5)	0/70 (0)	-
Contusion [a)]	First	124/910 (13.6)	41/902 (4.5)	-	-	41/902 (4.5)
	Second	85/909 (9.4)	33/899 (3.7)	-	-	33/899 (3.7)
Systemic						
Pyrexia	First	184/2588 (7.1)	22/2422 (0.9)	6/1476 (0.4)	0/49 (0)	16/897 (1.8)
	Second	23/1873 (1.2)	19/1765 (1.1)	3/813 (0.4)	0/63 (0)	16/889 (1.8)
Feverishness [a)]	First	546/1745 (31.3)	141/1593 (8.9)	122/1493 (8.2)	19/100 (19.0)	-
	Second	94/1011 (9.3)	46/895 (5.1)	45/825 (5.5)	1/70 (1.4)	-
Chills [a)]	First	544/1745 (31.2)	107/1593 (6.7)	101/1493 (6.8)	6/100 (6.0)	-
	Second	54/1011 (5.3)	37/895 (4.1)	34/825 (4.1)	3/70 (4.3)	-
Arthralgia	First	634/2655 (23.9)	242/2494 (9.7)	130/1493 (8.7)	8/100 (8.0)	104/901 (11.5)
	Second	195/1921 (10.2)	134/1794 (7.5)	61/825 (7.4)	1/70 (1.4)	72/899 (8.0)
Myalgia	First	1071/2655 (40.3)	463/2495 (18.6)	319/1493 (21.4)	21/100 (21.0)	123/902 (13.6)
	Second	364/1921 (18.9)	193/1794 (10.8)	111/825 (13.5)	3/70 (4.3)	79/899 (8.8)
Fatigue	First	1317/2655 (49.6)	834/2496 (33.4)	645/1493 (43.2)	25/100 (25.0)	164/903 (18.2)
	Second	515/1922 (26.8)	360/1796 (20.0)	238/825 (28.8)	8/70 (11.4)	114/901 (12.7)
Headache	First	1291/2655 (48.6)	844/2496 (33.8)	571/1493 (38.2)	43/100 (43.0)	230/903 (25.5)
	Second	514/1922 (26.7)	381/1796 (21.2)	203/825 (24.6)	14/70 (20.0)	164/901 (18.2)
Malaise [a)]	First	711/1745 (40.7)	267/1593 (16.8)	240/1493 (16.1)	27/100 (27.0)	-
	Second	172/1011 (17.0)	100/895 (11.2)	95/825 (11.5)	5/70 (7.1)	-
Nausea [a)]	First	353/1745 (20.2)	176/1593 (11.0)	164/1493 (11.0)	12/100 (12.0)	-
	Second	83/1011 (8.2)	64/895 (7.2)	62/825 (7.5)	2/70 (2.9)	-
Vomiting [a)]	First	24/1745 (1.4)	13/1593 (0.8)	11/1493 (0.7)	2/100 (2.0)	-
	Second	7/1011 (0.7)	3/895 (0.3)	3/825 (0.4)	0/70 (0)	-

N = number of participants analyzed; n = number of participants with events

a) The analysis excluded Study COV005 because, in Study COV005, events of injection site pain, feeling hot, induration, feverishness, chills, malaise, nausea, and vomiting were not collected or assessment criteria of the events were not compatible. The event of contusion was collected only in Study COV005.

In the Dose 1 SD for Safety Analysis Set (DCO2), the incidence of unsolicited AEs was 44.8% (4,625/10,317 participants) in the Vaxzevria group and 33.7% (3,421/10,141 participants) in the control group. The proportion of unsolicited AEs for which causal relationship with the study vaccine could not be ruled out was 36.2% (3,735/10,317 participants) in the Vaxzevria group and 23.0% (2,333/10,141 participants) in the control group.

In the Dose 1 SD for Safety Analysis Set (DCO2), unsolicited AEs observed in ≥1% of participants in either treatment group are shown in Table 27-1, and unsolicited AEs observed in ≥1% of participants in either treatment group after the first and second doses that were related to the study vaccine are shown in Tables 27-2 and 27-3.

Table 27-1 Unsolicited AEs Observed in ≥1% of participants in Either the Vaxzevria or Placebo Group during 28 Days after the Last Dose (Dose 1 SD for Safety Analysis Set, DCO2)

Event term PT (MedDRA/J Ver. 23.1)	Vaxzevria	Control			
		All controls combined	Meningococcal vaccine 2-dose	Meningococcal vaccine + placebo	Placebo 2-dose
	N = 10317	N = 10141	N = 3944	N = 5209	N = 988
	n (%)	n (%)	n (%)	n (%)	n (%)
Vaccination site pain	1471 (14.3)	902 (8.9)	91 (2.3)	811 (15.6)	0
Headache	1278 (12.4)	872 (8.6)	120 (3.0)	656 (12.6)	96 (9.7)
Myalgia	1031 (10.0)	425 (4.2)	41 (1.0)	364 (7.0)	20 (2.0)
Pyrexia	982 (9.5)	246 (2.4)	29 (0.7)	214 (4.1)	3 (0.3)
Fatigue	565 (5.5)	352 (3.5)	104 (2.6)	229 (4.4)	19 (1.9)
Chills	470 (4.6)	119 (1.2)	7 (0.2)	109 (2.1)	3 (0.3)
Asthenia	315 (3.1)	172 (1.7)	2 (0.1)	154 (3.0)	16 (1.6)
Malaise	302 (2.9)	167 (1.6)	48 (1.2)	119 (2.3)	0
Nausea	236 (2.3)	149 (1.5)	31 (0.8)	104 (2.0)	14 (1.4)
Cough	164 (1.6)	191 (1.9)	22 (0.6)	130 (2.5)	39 (3.9)
Pain	162 (1.6)	64 (0.6)	14 (0.4)	37 (0.7)	13 (1.3)
Arthralgia	161 (1.6)	94 (0.9)	38 (1.0)	44 (0.8)	12 (1.2)
Diarrhoea	160 (1.6)	148 (1.5)	27 (0.7)	112 (2.2)	9 (0.9)
Vaccination site erythema	142 (1.4)	171 (1.7)	15 (0.4)	152 (2.9)	4 (0.4)
Pain in extremity	131 (1.3)	86 (0.8)	44 (1.1)	37 (0.7)	5 (0.5)
Oropharyngeal pain	127 (1.2)	135 (1.3)	40 (1.0)	74 (1.4)	21 (2.1)
Influenza like illness	109 (1.1)	71 (0.7)	12 (0.3)	3 (0.1)	56 (5.7)
Rhinitis	105 (1.0)	137 (1.4)	3 (0.1)	134 (2.6)	0
Odynophagia	92 (0.9)	106 (1.0)	1 (<0.1)	105 (2.0)	0

N = number of participants analyzed; n = number of participants with events

Table 27-2 Unsolicited AEs Observed in ≥1% of participants in Either the Vaxzevria or Placebo Group during 28 Days after the First Dose That Were Related to the Study Vaccine (Dose 1 SD for Safety Analysis Set, DCO2)

Event term PT (MedDRA/J Ver. 23.1)	Vaxzevria	Control			
		All controls combined	Meningococcal vaccine 2-dose	Meningococcal vaccine + placebo	Placebo 2-dose
	N = 10317	N = 10141	N = 3944	N = 5209	N = 988
	n (%)	n (%)	n (%)	n (%)	n (%)
Vaccination site pain	1261 (12.2)	796 (7.8)	53 (1.3)	743 (14.3)	0
Headache	953 (9.2)	509 (5.0)	47 (1.2)	440 (8.4)	22 (2.2)
Pyrexia	906 (8.8)	188 (1.9)	14 (0.4)	173 (3.3)	1 (0.1)
Myalgia	895 (8.7)	307 (3.0)	21 (0.5)	281 (5.4)	5 (0.5)
Fatigue	432 (4.2)	222 (2.2)	54 (1.4)	163 (3.1)	5 (0.5)
Chills	415 (4.0)	91 (0.9)	2 (0.1)	87 (1.7)	2 (0.2)
Asthenia	253 (2.5)	116 (1.1)	1 (<0.1)	108 (2.1)	7 (0.7)
Malaise	250 (2.4)	108 (1.1)	23 (0.6)	85 (1.6)	0
Nausea	159 (1.5)	77 (0.8)	12 (0.3)	61 (1.2)	4 (0.4)
Pain	117 (1.1)	38 (0.4)	8 (0.2)	28 (0.5)	2 (0.2)
Arthralgia	110 (1.1)	40 (0.4)	10 (0.3)	27 (0.5)	3 (0.3)
Vaccination site erythema	109 (1.1)	159 (1.6)	10 (0.3)	146 (2.8)	3 (0.3)

N = number of participants analyzed; n = number of participants with events

Table 27-3 Unsolicited AEs Observed in ≥1% of participants in Either the Vaxzevria or Placebo Group during 28 Days after the Second Dose That Were Related to the Study Vaccine (Dose 1 SD for Safety Analysis Set, DCO2)

Study vaccine PT (MedDRA/J Ver. 23.1)	Vaxzevria	Control			
		All controls combined	Meningococcal vaccine 2-dose	Meningococcal vaccine + placebo	Placebo 2-dose
	N = 10317	N = 10141	N = 3944	N = 5209	N = 988
	n (%)	n (%)	n (%)	n (%)	n (%)
Vaccination site pain	361 (3.5)	129 (1.3)	38 (1.0)	91 (1.7)	-
Headache	189 (1.8)	140 (1.4)	34 (0.9)	93 (1.8)	13 (1.3)
Myalgia	109 (1.1)	51 (0.5)	16 (0.4)	32 (0.6)	3 (0.3)
Fatigue	103 (1.0)	65 (0.6)	36 (0.9)	23 (0.4)	6 (0.6)

N = number of participants analyzed; n = number of participants with events

By the time of the primary analysis (DCO2), deaths were reported in 2 participants in the Vaxzevria group (respiratory tract infection fungal and metastatic neoplasm) and 5 participants in the control group (COVID-19 pneumonia, craniocerebral injury, injury, homicide, and haematological malignancy). The causal relationship with the study vaccine was ruled out for all of these events. Adverse events resulting in withdrawal from the study were observed in 0 participants in the Vaxzevria group and 2 participants in the control group.

Serious adverse events were observed in 108/12,282 participants (0.9%) in the Vaxzevria group and 127/11,962 participants (1.1%) in the control group. Adverse events observed in ≥2 participants in either group were appendicitis (6 participants in the Vaxzevria group vs. 7 participants in the control group [the same order applies hereinafter]); diverticulitis (3 vs. 0); pancreatitis (3 vs. 0); adnexal torsion (2 vs. 0); angina pectoris (2 vs. 0); endometriosis (2 vs. 0); haemorrhagic ovarian cyst (2 vs. 0); intervertebral disc protrusion (2 vs. 0); meniscus injury (2 vs. 0); pyelonephritis (2 vs. 0); pyrexia (2 vs. 0); volvulus (2 vs. 0); abdominal pain (2 vs. 1); abortion spontaneous (2 vs. 1); calculus urinary (2 vs. 2); COVID-19 (2 vs. 17); nephrolithiasis (1 vs. 2); pericarditis (1 vs. 2); acute myocardial infarction (0 vs. 2); cholelithiasis (0 vs. 2); intentional overdose (0 vs. 2); pilonidal cyst (0 vs. 2); road traffic accident (0 vs. 2); sepsis (0 vs. 2); small intestinal obstruction (0 vs. 2); subarachnoid haemorrhage (0 vs. 2); syncope (0 vs 2); upper limb fracture (0 vs. 2); ureterolithiasis (0 vs. 2); wrist fracture (0 vs. 2); transient ischaemic attack (0 vs. 3), and COVID-19 pneumonia (0 vs. 4). Serious adverse events for which causal relationship with the study vaccine could not be ruled out were observed in 2 participants in the Vaxzevria group (pyrexia and myelitis transverse) (see Sections 7.R.3.1.2 and 7.R.3.2.2) and 2 participants in the control group (autoimmune haemolytic anaemia and myelitis).

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package and review policy

Under the COVID-19 pandemic, prompt development of SARS-CoV-2 vaccines is needed. To accelerate the development, ICMRA[15], WHO[16] and regulatory authorities in each country[17] have issued guidance on the development. In Japan, PMDA published the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2" (https://www.pmda.go.jp/files/000236327.pdf [last accessed on April 6, 2021]) on

15) ICMRA statement on COVID-19: International regulators pledge collective support to combat COVID-19 (http://www.icmra.info/drupal/news/statement_on_COVID-19 [Last accessed on April 6, 2021]), ICMRA statement on clinical trials: International regulators provide guidance on prioritization of COVID-19 clinical trials (http://www.icmra.info/drupal/news/statement_on_clinical_trials [Last accessed on April 6, 2021])

16) "WHO R&D Blueprint; Target Product Profiles for COVID-19 Vaccines. WHO; 2020" and "WHO R&D Blueprint; An international randomized trial of candidate vaccines against COVID-19. WHO; 2020"

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

September 2, 2020. The following concepts are mainly presented for clinical studies:

- The efficacy of infectious disease preventive vaccines is in principle evaluated using the disease-preventive effect as the primary endpoint. In the current situation in which no surrogate marker for the disease-preventive effect against COVID-19 is known, in principle, clinical trials to assess the preventive effect against COVID-19 must be conducted.
- The benefit-risk judgement of any SARS-CoV-2 vaccines can differ depending on the situation of each country/region, given that the degree of the COVID-19 epidemic, that the virus may undergo mutation according to the geographic/passage conditions, and that the percentage of severe patients with worsened COVID-19 differs considerably between different countries or regions. In addition, ethnic differences might affect the efficacy and safety of the SARS-CoV-2 vaccine. There may therefore be a high need of evaluating the efficacy and safety of the vaccine in Japanese participants by conducting a clinical trial(s) in Japan, even if a large-scale confirmatory trial is conducted overseas to evaluate the disease-preventive effect.
- When a large-scale confirmatory clinical trial of the 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 participants without conducting a confirmatory clinical trial in Japan to evaluate the disease-preventive effect in Japanese participants.

PMDA reached the following conclusion regarding the review policy for Vaxzevria, based on the review results presented in Sections 7.R.1.1 and 7.R.1.2:
At present, there are no surrogate endpoints for the protective effect against COVID-19 and the relationship between immunogenicity and the protective effect against COVID-19 remains unclear. However, because rapid development of SARS-CoV-2 vaccines is needed, PMDA decided to evaluate the efficacy and safety of Vaxzevria in the Japanese population based on (a) the efficacy and safety data from the pooled analysis of foreign studies that evaluated protective effect (handled as the pivotal study results) (see Section 7.R.1.1), and (b) the immunogenicity and safety data in the Japanese population in Japanese Study D8111C00002. In the United States, a phase III study (Study D8110C00001) is ongoing to evaluate the efficacy and safety of Vaxzevria, versus placebo, at 2 SD doses administered 4 weeks apart, in adults aged ≥18 years. Preliminary efficacy results will be available around April 2021. Therefore, although not included in the clinical data package for this application, the preliminary results of Study D8110C00001 will be examined by PMDA as soon as they become available.

7.R.1.1 Pooled analysis of 4 foreign studies

The applicant's explanation about the reasons and appropriateness of the pooled analysis of 4 foreign studies:
The 4 foreign studies (Studies COV001, COV002, COV003, and COV005) included in the pooled analysis are summarized in Table 28.

The original plan was to evaluate the 4 studies independently. However, because COVID-19 pandemic was rapidly spreading, this pooled analysis was planned to evaluate the efficacy of Vaxzevria at an earlier stage after

initiating the studies. For this pooled analysis, meeting with EMA and MHRA were started in [redacted] and [redacted] 20[redacted], respectively, and the Statistical Analysis Plan version [redacted] was prepared as of [redacted], 20[redacted]. Supplemental analyses were to be conducted at the end of each study without performing interim analysis of individual studies. Analyses of individual studies were not to be conducted before the pooled analysis.

Table 28 Pooled Analysis of 4 Foreign Studies

Study identifier	Study COV001[a)]	Study COV002[b)]	Study COV003[c)]	Study COV005[d)]
Country	UK	UK	Brazil	South Africa
Study initiation date Status	April 2020 Ongoing	May 2020 Ongoing	June 2020 Ongoing	June 2020 Ongoing
Phase	I/II	II/III	III	I/II
Study design	Single-blind, randomized, comparative study	Single-blind, randomized, comparative study	Single-blind, randomized, comparative study	Double-blind, randomized, comparative study
Target sample size	Approx. 1090	Approx. 12390	Approx. 10300	Approx. 2070
Age of participants included in pooled analysis	18-55 years	≥18 years	≥18 years	18-65 years
Participants	Healthy adults	Adults (with priority given to healthcare professionals and adults likely to be exposed to SARS-CoV-2)	Adults (with priority given to healthcare professionals and adults likely to be exposed to SARS-CoV-2)	Adults with or without HIV-infection
Main exclusion criteria for underlying diseases/conditions	・ Underlying disease, etc. ・ History of anaphylaxis or angioedema ・ History of allergic disease or reactions that can be exacerbated by any component of Vaxzevria or meningococcal vaccines	・ Severe and uncontrolled underlying diseases/conditions ・ Confirmed or suspected immunosuppressive or immunodeficient state ・ History of anaphylaxis or angioedema ・ History of allergic disease or reactions that can be exacerbated by any component of Vaxzevria or meningococcal vaccines		
Handling of pregnant or lactating women or women who plan/wish to become pregnant during the study period	Excluded from enrollment			
Main exclusion criteria related to COVID-19	・ History of laboratory-confirmed COVID-19 ・ New onset of pyrexia, cough, shortness of breath, etc. since February 2020 or SARS-CoV-2 antibody positive ・ High risk of contact with COVID-19 patients prior to enrollment ・ Living with a person at higher risk of severe COVID-19	・ History of laboratory-confirmed COVID-19 (except for Groups 5d, 9, 10, and 11)	・ History of laboratory-confirmed COVID-19 (serology, rapid antigen or antibody test, or nucleic acid amplification test) ・ SARS-CoV-2 antibody-positive before enrollment (not applicable in protocols ver. ≥[redacted])	・ Evidence of current SARS-CoV-2 infection detected by molecular assay detection of SARS-CoV-2 done within 96 hours prior to randomization ・ History of laboratory-confirmed COVID-19 or close contact (e.g., living together) with a person infected with SARS-CoV-2 ・ New onset of pyrexia, cough, or shortness of breath within 30 days prior to screening/enrollment
Number of doses of study vaccine (intramuscular injection)	1 or 2 doses (according to study group)	1 or 2 doses (according to study group)	2 doses	2 doses
Vaxzevria dosage	SD: 5×10^{10} vp LD: 2.5×10^{10} vp	SD: 5×10^{10} vp LD: 2.2×10^{10} vp	SD: 5×10^{10} vp	SD: 5×10^{10} vp LD: 2×10^{10} vp
Control	Meningococcal vaccine	Meningococcal vaccine	Dose 1: Meningococcal vaccine Dose 2: Placebo (physiological saline)	Placebo (physiological saline)
Dose interval	4-8 weeks	≥4 weeks	4-12 weeks	4 weeks
COVID-19 case detection	Passive	Passive and active (weekly nasal swab or saliva collection for	Passive	Passive and active (nasal swab at visits or saliva collection for SARS-CoV-2 nucleic acid

			SARS-CoV-2 nucleic acid amplification test)		amplification test)
Collection of safety information	Solicited AEs	· Participant diary in some participants · Collection period: 7 days after each dose (Day 0-7) · Same as Study COV002 for 7 local events and 10 systemic events	· Participant diary in some participants · Collection period: 7 days after each dose (Day 0-7) · Same as Study COV001 for 7 local events and 10 systemic events	· Participant diary in some participants · Collection period: 7 days after each dose (Day 0-7) · Similar terms used as Studies COV001 and COV002 for 7 local events and 10 systemic events	· Participant diary in some participants · Collection period: 6 days after each dose (Day 0-6) · The same or similar terms used as Studies COV001 and COV002 for 5 local events and 7 systemic events. However, some events (pain, feeling hot, malaise, nausea, vomiting) were not collected through the participant diary and bruising (which was not included in the protocol) was collected
	Unsolicited AEs	· Collection period: Up to 28 days after each dose	· Collection period: Up to 28 days after each dose	· Collection period: Up to 28 days after each dose	· Collection period: Up to 28 days after each dose
	Severity classification	FDA guidance: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (FDA, 2007)			NIH guidance: DAIDS grading the severity of adult and paediatric adverse events
Planned follow-up period		364 days after the last dose	364 days after the last dose	364 days after the last dose	364 days after the first dose

a) As of protocol version [redacted] ([redacted], 20[redacted])
b) As of protocol version [redacted] ([redacted], 20[redacted])
c) As of protocol version [redacted] ([redacted], 20[redacted])
d) As of protocol version [redacted] ([redacted], 20[redacted])

When the pooled analysis was planned, the US Study D8110C00001 and other studies were ongoing, in addition to the 4 Studies COV001, COV002, COV003, and COV005. The reason for selecting the 4 studies for the pooled analysis was that these studies started soon after serious SARS-CoV-2 pandemic began and therefore were progressing ahead. In addition, the studies were all sponsored by the University of Oxford and, as shown in Table 28, were similar in study design, data collection method, method of case confirmation of SARS-CoV-2 infection, and central assessment process. Therefore combining the studies for analysis was considered appropriate.

All 4 studies were designed as randomized controlled studies in principle in a manner to ensure blinding (single-blind for Studies COV001, COV002, and COV003 and double-blind for Study COV005), with similar endpoints (safety, immunogenicity, and efficacy) and similar study populations. There were some differences in the design of the 4 studies. Handling of the differences in analysis was pre-specified in the Statistical Analysis Plan for the pooled analysis, as shown below.

- The following are excluded from all analysis sets:
  - Groups that have not been randomized (e.g., Group 3 of Study COV001 and Group 11 of Study COV002)
  - Individuals who had received a ChAdOx1 vector vaccine in the past (e.g., Group 11 of Study COV002)
  - Individuals diagnosed with HIV-positive at the start of study (Group 12 of Study COV002 and Group 3 of Study COV005)
  - Individuals <18 years old

  In addition, the Vaxzevria groups that were not randomized in a 1:1 ratio to the concurrent control group (e.g., Groups 1, 2, 5, 7, and 8 in Study COV002), are excluded from the efficacy analysis set.

- The primary objective is to estimate the efficacy of 2 intramuscular doses of Vaxzevria with the second SD dose, versus control, for prevention of COVID-19 in adults aged ≥18 years (see Section 7.R.2.1.2).
- The primary efficacy analysis is based on the SDSD + LDSD seronegative efficacy analysis set. SD is defined as a dose of 5×10^{10} vp or equivalent viral particle. LD is defined as a dose of 2×10^{10} vp, 2.2×10^{10} vp, or 2.5×10^{10} vp (see Section 7.R.2.1.1).
- All analyses are performed separately for each dose of study vaccine actually administered.
- The primary efficacy endpoint was the first case of SARS-CoV-2 virologically-confirmed symptomatic COVID-19 occurring ≥15 days after the second dose of study vaccine. Cases were counted as events only if both (a) the sampling date of positive nucleic acid amplification test and (b) the onset date of COVID-19 symptom(s), were ≥15 days after the second dose. The date of event onset is either (a) the date of the nucleic acid amplification test or (b) the date of symptom onset, whichever is earlier, adjudicated by the endpoint adjudication committee for analysis. For participants with multiple events, only the first occurrence will be used for the analysis of primary efficacy endpoint (see Section 7.R.2.1.2).
- Solicited local AEs and solicited systemic AEs collected from Day 0 through Day 7 after study vaccination (i.e., the day of study vaccination and the following 7 days; [for Study COV005, the day of study vaccination and the following 6 days[18)]]), are separately summarized.
- Solicited AEs are combined taking into account of differences in the method of severity assessment between the studies, and the detailed method will be prespecified in the Statistical Analysis Plan for the pooled analysis. The guidance used for determining the severity of unsolicited AEs in Studies COV001, COV002, and COV003 was different from that used in Study COV005 (see Section 11.2). For the pooled analysis, all data combined from the 4 studies are classified according to the FDA guidance used in Studies COV001, COV002, and COV003.

The global team members of the applicant (AstraZeneca K.K.) who prepared the Statistical Analysis Plan for the pooled analysis had been blinded until the data safety monitoring committee declared the efficacy of Vaxzevria on [redacted], 20[redacted], and therefore they could not confirm the results of each study in advance. The unblinded data were only available to the independent biometrics team of the University of Oxford who performed the analyses for the data safety monitoring committee. Interim analysis data were provided only to the data safety monitoring committee. The committee was to notify the sponsor (the University of Oxford) whether the data met the predefined efficacy criteria.

Taking into consideration the above and the current pandemic of COVID-19, this pooled analysis is considered appropriate as a method to obtain the results of efficacy, safety, and immunogenicity necessary for judgment of the regulatory authorities.

PMDA's conclusion regarding the pooled analysis of the 4 foreign studies:
This pooled analysis was planned after the start of all 4 studies included in the pooled analysis, and there were differences in the study design such as dosing regimen and endpoints between the studies. In all of the studies, many amendments and changes were made to the dosing regimen, target sample size, etc. after the start of study

18) Due to an error in the interpretation of the protocol.

(see Section 11.3). However, considering the urgency for the development of Vaxzevria, it is understandable to some extent that there was no other choice but to formulate development strategies for Vaxzevria based on inadequate information, because at the time of planning the studies, there were uncertainties about SARS-CoV-2 infection status, optimal dosing regimen and evaluation method for Vaxzevria. Taking also account of the review in Section 7.R.2.1.1 and Section 2, PMDA considers that the designs of the 4 studies are similar enough to allow evaluation of the efficacy and safety of Vaxzevria using pooled data from the studies, assuming that similar immunogenicity is obtained regardless of dosing regimen, participant population, and study region. The applicant, who planned the pooled analysis, was blinded to all of the studies, and the pooled analysis plan was determined prior to the interim analysis (DCO1). In all of the 4 studies, COVID-19 events were adjudicated by a blinded independent endpoint adjudication committee in all participants with virologically confirmed SARS-CoV-2 infection. Thus, PMDA considers that the efficacy and safety of Vaxzevria can be evaluated based on the pooled analysis of the 4 foreign studies, and that the applicant had no choice but to combine data from the preceding 4 foreign studies in order to evaluate the efficacy and safety of Vaxzevria as soon as possible.

7.R.1.2 The clinical data package

The applicant's explanation about the clinical data package:
At the time of planning the Japanese clinical study of Vaxzevria, foreign large-scale studies to evaluate the protective effect were ongoing or expected to be started, and a Japanese clinical study to evaluate the protective effect was considered unfeasible because Japan had a relatively small number of COVID-19 cases. Therefore, the applicant planned to conduct a Japanese clinical study to confirm the immunogenicity and safety and compare its results with the safety and immunogenicity data from the foreign confirmatory studies.

In UK and Europe, in response to the serious public health emergencies associated with the spread of SARS-CoV-2 infection, it was decided to promptly evaluate the efficacy and safety of Vaxzevria based on a pooled analysis of the 4 ongoing foreign studies (Studies COV001, COV002, COV003, and COV005), in order to assess the efficacy and safety of Vaxzevria early and to provide MHRA and EMA with data that would allow them to make a decision on the use of vaccines at the end of 2020 or early 2021. Currently, a phase III study of Vaxzevria (Study D8110C00001) is ongoing mainly in US. If Study D8110C00001 is included the clinical data package for the application of Vaxzevria in Japan, the approval may be delayed. Therefore, the clinical data package for marketing application in Japan consists of (a) the pooled analysis of the 4 foreign studies, which is positioned as a pivotal study to evaluate the efficacy and safety of Vaxzevria, and (b) the Japanese clinical study.

PMDA's conclusion regarding the clinical data package:
In the situation where rapid development of vaccines is needed, considering the time when the results of US Study D8110C00001 become available, it is reasonable to use the results of pooled analysis of the 4 foreign studies as the primary data to evaluate the protective effect of Vaxzevria. Considering the discussion in Section 7.R.1.1, Vaxzevria can be reviewed based on the clinical data package submitted by the applicant.

The efficacy and safety data from the pooled analysis (see Section 7.4) were evaluated based on the following policy:

- One interim analysis and primary analysis for efficacy were planned (Statistical Analysis Plan version [redacted], dated [redacted], 20[redacted]), and the efficacy of Vaxzevria was demonstrated by the interim analysis (DCO1). Therefore, the results of the interim analysis (DCO1) were positioned as confirmatory results of efficacy in the pooled analysis, and the results of the primary analysis (DCO2) were positioned as a supplement to the interim analysis (DCO1). Nevertheless, the primary analysis (DCO2) population was observed for a longer period of time and included more participants with more diverse characteristics than the interim analysis (DCO2) population. Therefore, although the primary efficacy was evaluated based on the results of the interim analysis (DCO1), the detailed efficacy and safety were evaluated based on the results of the primary analysis (DCO2).
- The safety profile of Vaxzevria was evaluated based on the results in the Dose 1 SD for Safety Analysis Set. The results in the Any Dose for Safety Analysis Set were evaluated to assess serious adverse events (SAEs) and adverse events of special interest (AESIs). Solicited AEs were evaluated in participants in the Dose 1 SD for Safety Analysis Set who experienced solicited AEs recorded in the participant diary (these participants were regarded as participants experiencing with solicited AEs following Dose 1 SD).
- Efficacy control group

  Because of difference in the feasibility of clinical studies between different countries, the pooled analysis included different control groups: the meningococcal vaccine 2-dose group; the meningococcal vaccine (first dose) and placebo (second dose) group; and the placebo 2-dose group. However, none of the control vaccines contain an active substance against SARS-CoV-2, and none are likely to affect (a) the exposure to risks of SARS-CoV-2 infection or (b) the onset or course of COVID-19. Therefore, in the pooled analysis, different control groups were combined into a single efficacy control group, based on which the efficacy was evaluated.
- Safety control group

  In the application dossier, different control groups were combined and handled as a single safety control group, as with the efficacy control group. However, PMDA considered that the active and placebo control groups should be separated from each other when evaluating the safety. Thus, the safety was evaluated after dividing the single control group into 3 groups: the meningococcal vaccine 2-dose group, the meningococcal vaccine (first dose) and placebo (second dose) group, and the placebo 2-dose group.

7.R.2 Efficacy

7.R.2.1 Primary efficacy evaluation

In the pooled analysis, the primary efficacy analysis set included participants who were seronegative at baseline, received LDSD or SDSD, did not have SARS-CoV-2 virologically confirmed COVID-19[19)] for 15 days after the second dose, and had follow-up data starting ≥15 days after the second dose. The primary efficacy endpoint was the first case of SARS-CoV-2 virologically confirmed symptomatic COVID-19 occurring ≥15 days after the second dose of study vaccine.

The following items related to the primary efficacy evaluation were examined.

19) Confirmed by RT-PCR or other nucleic acid amplification test

7.R.2.1.1 The primary efficacy analysis set is defined as population receiving LDSD or SDSD

The applicant explained the reason for selecting the population receiving LDSD or SDSD as the primary efficacy analysis set in the pooled analysis.

The applicant's explanation:

The Vaxzevria dose selected for the first clinical study of Vaxzevria, Study COV001, was 5×10^{10} vp per dose (SD), because this dose was shown to be well-tolerated and the most immunogenic in previous clinical studies of ChAdox1-vectored vaccines (see Section 7.R.6.1). In addition, some groups of participants received 2 doses and the second dose was either SD or 2.5×10^{10} vp (LD) to save the dose (Section 7.1.2, *Nat Med*. 2021;27:279-88). Study COV002 was designed to administer SD as the second dose to participants who received SD as the first dose, and LD as the second dose to participants who received LD as the first dose (*Lancet*. 2020;396:1979-93). However, during the study, an unintended error in dose was found (see Section 11.5), resulting in the dose groups of SD, LD, SDSD, LDSD, and LDLD (see Section 7.2.1). There was an unintended dose error also in Study COV005, resulting in the dose groups of SD, LD, SDSD, LDSD, and LDLD (see Sections 7.1.3 and 11.5).

In Study COV002, LD and SD of Vaxzevria showed similar immunogenicity data at Day 28 after the first dose, with no substantial difference between LD (single dose) and SD (single dose) in neutralizing antibody titers within each subgroup of 18 to 55, 56 to 69, and ≥70 years old (*Lancet.* 2020;396:1979-93). Thus, there was no meaningful difference between the first SD dose and the first LD dose. Since inclusion of participants receiving the first LD dose in analysis increases the number of evaluable participants and the likelihood of detecting an efficacy signal earlier, the LDSD and SDSD data were combined for the primary efficacy endpoint analysis.

PMDA's view:

The applicant made a plan to combine the LDLD and SDSD groups into a single group for primary efficacy analysis, based on the immunogenicity results after a single dose of Vaxzevria. This plan is understandable, taking into account the applicant's explanation. The appropriateness of combining both groups into a single group is discussed again based on the efficacy and immunogenicity results from the pooled analysis in Section 7.R.2.2.1.2.

7.R.2.1.2 Primary endpoint

The primary objective of the pooled analysis was to evaluate the efficacy of Vaxzevria by comparing the protective effect against COVID-19 in adults aged ≥18 years between the Vaxzevria group and the control group. The primary endpoint was the incidence of first SARS-CoV-2 virologically confirmed symptomatic COVID-19 occurring ≥15 days post second dose. The applicant explained the primary endpoint as follows:

[1] Protective effect against COVID-19 selected as the primary endpoint

Requirements for clinical studies to evaluate SARS-CoV-2 vaccine candidates were agreed by the regulatory authorities in June 2020 at the ICMRA workshop co-chaired by EMA and FDA, and the recommended primary endpoint is "laboratory-confirmed COVID-19 of any severity" (http://www.icm ra.info/drupal/covid-19/vaccines_confidence_statement_for_hcps [last accessed on April 6, 2021]). Subsequently, WHO and EMA

issued similar recommendations[20]. Thus, the primary efficacy endpoint for the University of Oxford clinical studies was SARS-CoV-2 virologically confirmed symptomatic COVID-19 of any severity.

Asymptomatic SARS-CoV-2 infection is not considered as having an onset of the disease and is not included in the primary endpoint. In addition, if the efficacy evaluation is performed only on severe COVID-19 cases, a very large study is required to obtain adequate power, and therefore the conduct of such study is infeasible. Since the prevention of mild to moderate COVID-19 is important from the viewpoint of public health, defining the primary endpoint as "symptomatic COVID-19 of any severity" was appropriate.

[2] Evaluation period

The evaluation period for the primary efficacy endpoint was defined as "the period starting ≥15 days after the second dose" because, considering the time to achieve the immune response, the vaccine is considered to exert sufficient biological effect in this period, allowing for adequate evaluation of its benefits. This decision is not based on clinical data but is considered appropriate in view of the description in WHO guidance, "The analysis of the primary endpoint should include the first COVID-19 episode occurring more than 14 days after the first dose in each participant."[21]

[3] Definition of COVID-19 events (the primary endpoint)

COVID-19 events were defined as "virologically confirmed SARS-CoV-2 infection with at least one of the symptoms of pyrexia (≥37.8°C), cough, shortness of breath, anosmia, or ageusia, and confirmed by the endpoint adjudication committee." Cases were counted as events only if both (a) the sampling date of positive nucleic acid amplification test and (b) the onset date of COVID-19 symptom(s), were ≥15 days post second dose. The clinical symptoms of COVID-19 in this primary endpoint were determined based on the UK Public Health Agency and WHO guidelines[22] and an analysis by experts at the early stage of the global pandemic of COVID-19. This definition of COVID-19 has the sensitivity and specificity necessary to appropriately identify and confirm COVID-19 cases and to ensure the power of a clinical study and the clinical usefulness of the vaccine. The definition is also considered to reflect the events to be prevented by Vaxzevria based on the expected protective effect of vaccines against infection and public health necessity. In addition, these clinical symptoms (pyrexia ≥37.8°C, cough, shortness of breath, anosmia, or ageusia) are frequently used to identify cases of suspected COVID-19 in clinical practice.

[4] Use of multiple nucleic acid amplification methods for virological confirmation of SARS-CoV-2 infection

Virological confirmation of SARS-CoV-2 infection was based on RT-PCR alone in Studies COV003 and COV005. However, when the University of Oxford initiated Studies COV001 and COV002, there was insufficient supply of test reagents, and therefore, which nucleic acid amplification method is used for virological

20) Considerations for the Assessment of COVID-19 Vaccines – Points to consider for manufacturers of COVID-19 vaccines. WHO; 2020 EMA considerations on COVID-19 vaccine approval. EMA; 2020
21) WHO R&D Blueprint: novel Coronavirus. An international randomized trial of candidate vaccines against COVID-19. WHO; 2020
22) https://www.gov.uk/government/publications/covid-19-stay-at-home-guidance/stay-at-home-guidance-for-households-with-possible-coronavirus-covid-19-infection#symptoms (Last accessed on April 6, 2021) and https://www.who.int/health-topics/coronavirus#tab=tab_3 (Last accessed on April 6, 2021)

confirmation was determined at each site. As a result, in Studies COV001 and COV002, COVID-19 cases were virologically confirmed with 18 types of RT-PCR and 1 type of TMA. All of these tests were validated or qualified, and where possible, reagents approved as *in vitro* diagnostics by EMA self-certification process were used. Moreover, given the sufficiently high sensitivity and specificity of these tests (sensitivity, 80% to 100%; specificity, 93.07% to 100%), the use of multiple nucleic acid amplification methods for virological confirmation is unlikely to affect the evaluation of the efficacy of Vaxzevria, and the results of different test methods can be evaluated in the same manner.

[5] Method of COVID-19 event extraction

COVID-19 events were extracted for efficacy evaluation by a consistent method across the studies included in the pooled analysis. The inclusion criteria for the primary endpoint assessment based on the central assessment were as follows:

- Participants presenting with symptoms (pyrexia, cough, shortness of breath, anosmia, or ageusia) during the follow-up period are instructed to call the study team and receive advice on the procedure to undergo the COVID-19 test as necessary.
- At the visit for COVID-19 test, a nasal/throat swab and/or saliva sample, blood samples for safety and immunogenicity assay, vital signs, and other clinical information are collected.

With more epidemiological and pathological data on COVID-19 became available, the event definition and confirmation method were revised during the studies, as shown in Tables 57 to 60 in Section 11.3. However, these minor changes in the event definition or confirmation method are unlikely to have significantly affected the evaluation of efficacy or caused bias, because the studies were conducted in a blinded manner in the situation where there were no treatment options for early disease stages. For the central assessment, a common independent endpoint assessment committee was established for all 4 studies, and assessment of COVID-19 cases was performed in a blinded manner according to the predefined criteria for all participants with virologically confirmed SARS-CoV-2 infection. Therefore, scientific consistency and coherence across the studies were secured.

[6] Use of both passive and active sampling for the sampling method of virological test

In the 4 studies included in the pooled analysis, passive sampling, which is mentioned in [5] above, was performed on those who presented with symptoms suspected of COVID-19 defined in the protocol of each study.

On the other hand, in Study COV002, in addition to passive sampling, active sampling was performed by participants themselves on a weekly basis depending on the feasibility at test facilities, etc. If any symptom developed in participants who underwent active sampling, the participants were required to follow the procedures for symptomatic participants (visit for COVID-19 test, sample collection for nucleic acid amplification test, etc.). In Study COV005, active sampling with nasal swab and/or saliva was performed at every scheduled visit in order to maximize the detection of infection.

In infectious diseases with no available treatments, early detection is unlikely to influence the course or development of symptoms. Since these studies are blinded, randomized studies, factors other than the study vaccine (e.g., minor changes in case definition and case confirmation methods) have little influence on the difference between the Vaxzevria and control groups in the course of symptomatic SARS-CoV-2 infection. In addition, whether participants (including those with positive self-collected samples) met the criteria for the primary endpoint was adjudicated by the blinded independent endpoint adjudication committee after reviewing the data. Therefore, scientific consistency was secured among the studies, and active sample collection in Studies COV002 and COV005 is unlikely to have affected the efficacy evaluation of Vaxzevria.

PMDA's conclusion on the primary endpoint:
According to the "Vaccination Against COVID-19 (Cabinet Secretariat, the Ministry of Health, Labour and Welfare, February 9, 2021)" (https://www.cas.go.jp/jp/seisaku/ful/bunkakai/wakuchin_sesyu.pdf [last accessed on April 6, 2021]), the objective of SARS-CoV-2 vaccination is "to prevent COVID-19, minimize the number of deaths and severe cases, and consequently prevent the spread of COVID-19." Considering the current SARS-CoV-2 pandemic, preventing COVID-19 is important from the viewpoint of public health, and reducing the incidence will lead to the suppression of the number of severe cases. Therefore, it was appropriate to set the primary endpoint for the pooled analysis as protective effect against symptomatic COVID-19. The protective effect against severe COVID-19 was investigated as a secondary endpoint and is reviewed in Section 7.R.2.3.

As for the primary endpoint, the definition of COVID-19 events was not largely different from that recommended in international guidelines, etc., and there seems to have been no major problem in the evaluation of the efficacy of Vaxzevria. Whether the selected evaluation period (i.e., on and after 15 days post second dose) is optimal for evaluating the protective effect of Vaxzevria remains unclear. However, this evaluation period is understandable to a certain extent, given WHO guidelines advising that vaccine efficacy (VE) be evaluated >14 days after the last dose of a vaccine with a multiple-dose regimen[23)].

The use of different types of nucleic acid amplification test methods for virological confirmation of SARS-CoV-2 infection is considered practically inevitable. In normal circumstances, the appropriate measure is to introduce a standardized test method or central testing. However, the testing system was not fully in place at the time when the foreign studies began out of a need to accelerate vaccine development amid the pandemic. The use of different types of test methods does not pose a major problem in evaluating the efficacy of Vaxzevria taking into account the sensitivity, specificity, etc. of these tests.

As a rule, the definition of symptoms triggering virological testing to confirm COVID-19 should not be changed during the conduct of study. However, the definition of symptoms triggering virological testing had to be changed based on newly available epidemiological data and findings on pathology of COVID-19 collected; this is understandable. Furthermore, all studies were conducted in a blinded manner with a concurrent control, and each case was counted as an event meeting the criteria for the primary endpoint after being confirmed to have

23) WHO R&D Blueprint: novel Coronavirus. An international randomized trial of candidate vaccines against COVID-19. WHO; 2020

SARS-CoV-2 infection and upon confirmation by the blinded endpoint adjudication committee. In addition, the change in the definition of trigger symptoms occurred only in Study COV001, and that was immediately after the start of enrollment. Therefore, the change has little impact on the efficacy evaluation. Active sampling leads to viral testing in not only cases with triggering symptoms but also cases without symptoms; however, only cases with the predefined symptoms are counted as primary endpoint events. Thus, the use of both passive and active sampling for virological testing has little impact on the efficacy evaluation.

7.R.2.2 Efficacy results

7.R.2.2.1 Efficacy in the foreign pooled analysis

The applicant provided the following explanation about the efficacy of Vaxzevria against COVID-19.

7.R.2.2.1.1 Protective effect against COVID-19 in the foreign pooled analysis

Table 29 shows the results of VE of Vaxzevria against the first SARS-CoV-2 virologically confirmed COVID-19 occurring ≥15 days post second dose, which was the primary endpoint in the pooled analysis. In both the interim (DCO1) and primary (DCO2) analyses, the lower limit of the 2-sided 95.84% CI or 95% CI for VE was above the prespecified efficacy threshold of 20% in the SDSD + LDSD Seronegative for Efficacy Analysis Set. The applicant considers that the efficacy of Vaxzevria was demonstrated by the interim analysis (DCO1), and the conclusion of the interim analysis (DCO1) was reinforced by the subsequent primary analysis (DCO2).

Table 29 Interim Analysis (DCO1) and Primary Analysis (DCO2) for VE Against the First COVID-19 Occurring ≥15 Days Post Second Dose (Primary Endpoint)

	Vaxzevria		Control		VE%
	N	Events, n (%)	N	Events, n (%)	[2-sided 95.84% CI][a)]
DCO1: Study COV002 + Study COV003					
Primary analysis set SDSD + LDSD, seronegative	5807	30 (0.52)	5829	101 (1.73)	70.42 [54.84, 80.63]
ITT SDSD + LDSD, seronegative	5814	31 (0.53)	5831	100 (1.71)	69.13 [53.10, 79.68]
SDSD, seronegative	4440	27 (0.61)	4455	71 (1.59)	62.10 [39.96, 76.08]
LDSD, seronegative	1367	3 (0.22)	1374	30 (2.18)	90.05 [65.84, 97.10]
DCO2: Study COV001 + Study COV002 + Study COV003 + Study COV005					
Primary analysis set SDSD + LDSD, seronegative	8597	84 (0.98)	8581	248 (2.89)	66.73 [57.41, 74.01][b)]
ITT SDSD + LDSD, seronegative	8603	86 (1.00)	8586	246 (2.87)	65.65 [56.11, 73.11][b)]
SDSD, seronegative	7201	74 (1.03)	7179	197 (2.74)	63.09 [51.81, 71.73][b)]
LDSD, seronegative	1396	10 (0.72)	1402	51 (3.64)	80.31 [60.77, 91.09][b)]

N = number of participants analyzed; n = number of participants with events

a) Poisson regression with study identifier, vaccine group, and age at screening (18 to 55, 56 to 69, ≥70 years) as factors and the log of the follow-up period as an offset variable

b) Two-sided 95% CI

Table 30 shows the efficacy results by subgroup in the SDSD + LDSD Seronegative for Efficacy Analysis Set at the primary analysis (DCO2).

VE by country: Vaxzevria's protective effect against COVID-19 was demonstrated in the UK and Brazilian subgroups of the SDSD + LDSD Seronegative for Efficacy Analysis Set. The point estimates of VE tended to be higher in participants in UK than in those in Brazil, probably due to the larger number of participants with a longer dose interval in UK (the proportion of participants with a dose interval of ≥9 weeks in the Vaxzevria group, 71.0% in UK vs. 12.3% in Brazil) (see Section 7.R.2.2.1.3). In the South African subgroup (the proportion of participants with a dose interval of ≥9 weeks in the Vaxzevria group, 0.5%), there were only a small number of events qualified for VE assessment.

There were only a small number of events qualified for VE assessment also in subgroups of participants ≥65 years old and those 55 to 64 years old, and non-white participants. VE was similar between adults with underlying disease and other subgroups.

Table 30 Results of VE against First Case of SARS-CoV-2 Virologically Confirmed Symptomatic COVID-19 Occurring ≥15 Days Post Second Dose (SDSD + LDSD Seronegative for Efficacy Analysis Set, DCO2)

		Vaxzevria (number of participants)		Placebo (number of participants)		VE [2-sided 95% CI] (%)
		N (%)	Confirmed COVID-19, n (n/N)	N (%)	Confirmed COVID-19, n (n/N)	
All		8597 (100)	84 (0.98)	8581 (100)	248 (2.89)	66.73 [57.41, 74.01][c)]
Age	18-64 years	7894 (91.8)	80 (1.01)	7901 (92.1)	240 (3.04)	67.15 [57.70, 74.49][d)]
	≥65 years	703 (8.2)	4 (0.57)	680 (7.9)	8 (1.18)	51.91 [-59.98, 85.54][d)]
	18-54 years	7062 (82.1)	73 (1.03)	7046 (82.1)	226 (3.21)	68.32 [58.76, 75.66][d)]
	55-64 years	832 (9.7)	7 (0.84)	855 (10.0)	14 (1.64)	47.78 [-29.60, 78.96][d)]
	≥65 years	703 (8.2)	4 (0.57)	680 (7.9)	8 (1.18)	51.91 [-59.98, 85.54][d)]
Sex	Male	3781 (44.0)	28 (0.74)	3701 (43.1)	101 (2.73)	73.19 [59.25, 82.36][d)]
	Female	4816 (56.0)	56 (1.16)	4880 (56.9)	147 (3.01)	62.01 [48.33, 72.07][d)]
Race[a)]	White	6443 (74.9)	68 (1.06)	6556 (76.4)	202 (3.08)	66.17 [55.47, 74.29][d)]
	Black	872 (10.1)	6 (0.69)	820 (9.6)	10 (1.22)	44.79 [-51.92, 79.93][d)]
	Asian	320 (3.7)	0 (0)	285 (3.3)	16 (5.61)	100 [76.91, NE][e), f)]
	Mixed	358 (4.2)	8 (2.23)	359 (4.2)	6 (1.67)	-22.29 [-251.07, 57.40][d)]
	Other	592 (6.9)	2 (0.34)	548 (6.4)	13 (2.37)	85.45 [35.32, 96.73][d)]
Country	UK	4427 (51.5)	33 (0.75)	4521 (52.7)	133 (2.94)	75.20 [63.71, 83.06][d)]
	Brazil	3414 (39.7)	49 (1.44)	3339 (38.9)	112 (3.35)	57.61 [40.73, 69.68][d)]
	South Africa	756 (8.8)	2 (0.26)	721 (8.4)	3 (0.42)	37.04 [-277.20, 89.49][e), f)]
Comorbidities[b)]	Yes	3056 (35.5)	34 (1.11)	3102 (36.1)	93 (3.00)	62.71 [44.79, 74.82][d)]
	No	5241 (61.0)	50 (0.95)	5156 (60.1)	149 (2.89)	67.70 [55.51, 76.55][d)]

N = number of participants analyzed; n = number of participants with events; NE = not evaluable

a) Arabic was counted as white. A total of 12 participants (11 unknown, 1 without data) in the Vaxzevria group and 13 participants (11 unknown, 2 without data) in the control group are not included in the race category.

b) Participants with baseline BMI ≥30 kg/m^2, cardiovascular abnormalities, respiratory diseases, or diabetes were classified as "Yes." Because of lack of data, 300 participants in the Vaxzevria group and 323 participants in the control group are not included.

c) Poisson regression with the study identifier, vaccine group, and age at screening (18 to 55, 56 to 69, ≥70 years) as factors and the log of the follow-up period as an offset variable

d) Poisson regression with vaccine group as factor and the log of the follow-up period as an offset variable

e) Poisson regression with exact conditional method with vaccine group as factor

f) One-sided 97.5% CI

PMDA's conclusion:

Table 29 shows the lower limit of the 2-sided 95.84% CI for VE in the SDSD + LDSD Seronegative for Efficacy Analysis Set in the interim analysis (DCO1) of the foreign pooled analysis. Although whether the prespecified criterion for the lower limit (20%) is appropriate remains unclear, the efficacy of Vaxzevria was demonstrated because VE was higher than the lower limit shown in the FDA guidelines (30%).[24)] In addition, both (a) the analysis in the SDSD + LDSD Seronegative Efficacy ITT Analysis Set (based on randomized treatment groups regardless of study discontinuation), which is similar to the primary analysis (DCO2), and (b) the subgroup analysis by vaccination regimen, showed results similar to those of the interim analysis (DCO1).

Demonstrating the efficacy in every subgroup is difficult because some subgroups have only a very small number of participants. However, given the immunogenicity results (see Sections 7.R.2.2.1.2 and 7.R.2.2.3), the tendency in the efficacy results in the subgroups do not differ considerably from that in the overall population. Thus, Vaxzevria will provide promising benefits in the pandemic situation. However, the results by country show a low VE in the South African subgroup than in the other subgroups; this is discussed in Section 7.R.2.4. In addition, the accuracy of VEs in each subgroup needs to be re-evaluated when more data become available including the results from the US Study D8110C00001.

24) Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19. FDA;2020. WHO R&D Blueprint: novel coronavirus. An international randomized trial of candidate vaccines against COVID-19. WHO; 2020, etc.

Furthermore, because of the limited efficacy follow-up period in the pooled analysis (64.1 ± 29.86 days [mean ± SD] in the Vaxzevria group in the SDSD + LDSD Seronegative for Efficacy Analysis Set from DCO2) and the lack of long-term efficacy data, duration of efficacy should be investigated in the post-marketing setting.

The results of pooled analysis by age, dose interval, and vaccination regimen (SDSD and LDSD) are discussed in Sections 7.R.2.2.3, 7.R.2.2.1.3, and 7.R.2.2.1.2, respectively.

7.R.2.2.1.2 Immunogenicity data in the foreign pooled analysis

The applicant provided the following explanation about immunogenicity data in the pooled analysis:

[1] Humoral immunity

Table 31 shows neutralizing antibody titers against SARS-CoV-2 in the pooled analysis by vaccination regimen subgroup in the Immunogenicity Analysis Set. In the SDSD + LDSD Immunogenicity Analysis Set, participants who were seronegative at baseline showed an increase in neutralizing antibody titers 28 days after the first dose and a more pronounced increase 28 days after the second dose.

Table 31 Neutralizing Antibody Titers against SARS-CoV-2 in the Pooled Analysis (Neutralizing Antibody Assay Using Pseudovirus) (Immunogenicity Analysis Set, Seronegative, DCO2)

Timing of assay		SDSD + LDSD		SDSD	LDSD
		Vaxzevria	Control	Vaxzevria	Vaxzevria
	N	2122	1569	1746	376
28 days after the first dose	n/N_{sub}	801/2079	684/1536	652/1706	149/373
	GMT	**60.081**	**20.817**	**61.266**	**55.162**
	[2-sided 95% CI]	[54.91, 65.74]	[20.25, 21.39]	[55.46, 67.68]	[44.61, 68.21]
28 days after the second dose	n/N_{sub}	834/2079	683/1536	676/1706	158/373
	GMT	**180.881**	**21.721**	**174.773**	**209.516**
	[2-sided 95% CI]	[167.07, 195.83]	[20.93, 22.55]	[159.73, 191.23]	[177.48, 247.34]

N = number of participants per subgroup; n = number of participants evaluated

Table 32 shows neutralizing antibody titers against SARS-CoV-2 by race. Neutralizing antibody titers increased in all race subgroups after the first and second doses of Vaxzevria.

Table 33 shows neutralizing antibody titers against SARS-CoV-2 by country. Participants in Brazil had lower neutralizing antibody GMTs after the second dose than those in UK and South Africa. Differences in neutralizing antibody titers between the UK and Brazilian populations may have been confounded by dose interval (see Section 7.R.2.2.1.3). High levels of humoral immunity were observed in participants in South Africa; the reasons remain unclear, but hypotheses include cross-reactivity to baseline seasonal coronavirus, genetic factors, and trained immunity (*J Glob Health.* 2020;10: 020348, *Int J Infect Dis.* 2021; 102: 577).

Table 32 Neutralizing Antibody Titers against SARS-CoV-2 by Race in the Pooled Analysis (Neutralizing Antibody Assay Using Pseudovirus) (Immunogenicity Analysis Set, Seronegative, DCO2)

Race	Timing of assay		SDSD + LDSD		SDSD
			Vaxzevria	Control	Vaxzevria
		N	2077	1534	1704
White	28 days after the first dose	n/N_{sub}	607 / 1665	484 / 1173	474 / 1322
		GMT	**53.996**	**20.346**	**54.429**
		[2-sided 95% CI]	[48.85, 59.68]	[19.93, 20.77]	[48.69, 60.85]
	28 days after the second dose	n/N_{sub}	632 / 1665	486 / 1173	491 / 1322
		GMT	**171.398**	**21.600**	**161.840**
		[2-sided 95% CI]	[156.42, 187.81]	[20.72, 22.51]	[145.54, 179.96]
Black	28 days after the first dose	n/N_{sub}	96 / 158	107 / 157	92 / 153
		GMT	**107.630**	**22.167**	**107.335**
		[2-sided 95% CI]	[81.15, 142.75]	[19.97, 24.60]	[80.08, 143.87]
	28 days after the second dose	n/N_{sub}	108 / 158	105 / 157	104 / 153
		GMT	**258.871**	**23.456**	**255.909**
		[2-sided 95% CI]	[207.95, 322.26]	[20.31, 27.09]	[204.21, 320.69]
Asian	28 days after the first dose	n/N_{sub}	41 / 89	25 / 61	30 / 71
		GMT	**68.286**	**20.000**	**66.238**
		[2-sided 95% CI]	[43.42, 107.40]	[NE, NE]	[37.43, 117.21]
	28 days after the second dose	n/N_{sub}	40 / 89	24 / 61	29 / 71
		GMT	**152.788**	**20.000**	**148.913**
		[2-sided 95% CI]	[106.96, 218.25]	[NE, NE]	[97.46, 227.53]
Mixed	28 days after the first dose	n/N_{sub}	16 / 60	21 / 49	16 / 56
		GMT	**55.479**	**20.000**	**55.479**
		[2-sided 95% CI]	[29.33, 104.93]	[NE, NE]	[29.33, 104.93]
	28 days after the second dose	n/N_{sub}	18 / 60	22 / 49	17 / 56
		GMT	**196.745**	**20.000**	**204.227**
		[2-sided 95% CI]	[115.39, 335.45]	[NE, NE]	[116.37, 358.40]
Other	28 days after the first dose	n/N_{sub}	40 / 105	46 / 94	39 / 102
		GMT	**69.766**	**23.833**	**69.403**
		[2-sided 95% CI]	[46.92, 103.74]	[18.56, 30.60]	[46.19, 104.29]
	28 days after the second dose	n/N_{sub}	35 / 105	45 / 94	34 / 102
		GMT	**180.728**	**21.017**	**172.054**
		[2-sided 95% CI]	[120.77, 270.45]	[19.02, 23.23]	[115.03, 257.34]

N = number of participants per subgroup; n = number of participants evaluated; NE = not evaluable

Table 33 Neutralizing Antibody Titers against SARS-CoV-2 by Country in the Pooled Analysis (Neutralizing Antibody Assay Using Pseudovirus) (Immunogenicity Analysis Set, Seronegative, DCO2)

Country	Timing of assay		SDSD + LDSD		SDSD
			Vaxzevria	Control	Vaxzevria
		N	2079	1536	1706
UK	28 days after the first dose	n/N_{sub}	499/1474	378/944	353/1104
		GMT	**53.218**	**20.221**	**52.572**
		[2-sided 95% CI]	[47.67, 59.41]	[19.91, 20.54]	[46.26, 59.74]
	28 days after the second dose	n/N_{sub}	527/1474	375/944	372/1104
		GMT	**187.482**	**21.403**	**179.318**
		[2-sided 95% CI]	[170.26, 206.44]	[20.45, 22.40]	[159.49, 201.61]
Brazil	28 days after the first dose	n/N_{sub}	217/495	205/486	217/495
		GMT	**61.870**	**20.752**	**61.870**
		[2-sided 95% CI]	[52.13, 73.43]	[19.71, 21.85]	[52.13, 73.43]
	28 days after the second dose	n/N_{sub}	205/495	206/486	205/495
		GMT	**133.883**	**21.091**	**133.883**
		[2-sided 95% CI]	[112.61, 159.18]	[20.12, 22.11]	[112.61, 159.18]
South Africa	28 days after the first dose	n/N_{sub}	85/110	101/106	82/107
		GMT	**113.627**	**23.351**	**115.361**
		[2-sided 95% CI]	[83.57, 154.49]	[20.26, 26.91]	[83.94, 158.54]
	28 days after the second dose	n/N_{sub}	102/110	102/106	99/107
		GMT	**275.149**	**24.335**	**275.588**
		[2-sided 95% CI]	[223.86, 338.19]	[20.73, 28.56]	[223.01, 340.57]

N = number of participants per subgroup; n = number of participants evaluated

PMDA requested that the applicant explain the appropriateness of handling the LDSD population and the SDSD population as a single group on the basis of the efficacy and immunogenicity data from the pooled analysis.

The applicant' explanation:

For the pooled analysis, the population receiving the first and second SD doses (SDSD) and the population

receiving the first LD dose and the second SD dose (LDSD) were planned to be handled as a single population in the SDSD + LDSD Seronegative for Efficacy Analysis Set, which is the primary analysis set (see Section 7.R.2.1.1). VE differed between the 2 vaccination regimens (see Section 7.R.2.2.1.1), whereas CIs overlapped, and the difference is probably due to the dose interval (see Section 7.R.2.2.1.3). Thus, there is no evidence that the difference in efficacy is attributable to the dose level of the first dose. Of note, all participants in the LDSD group were non-elderly people.

As for the immunogenicity data, the pseudovirus neutralizing antibody titers in participants receiving 2 doses at an 8- to 12-week interval, were similar between the SDSD analysis set and the LDSD analysis set. (The LDSD group had few participants who received 2 doses at a ≤8-week interval.) (See Table 35 in Section 7.R.2.2.1.3).

Based on the above, it was appropriate to handling participants who received the second SD dose, irrespective of the first LD or SD dose, as a single primary analysis set.

PMDA also requested that the applicant explain the relationship between the protective effect of Vaxzevria against COVID-19 and neutralizing antibody titers.

The applicant's explanation:
The immunogenicity was evaluated in the pooled analysis only in a limited number of participants. As of February 26, 2021, the pseudovirus neutralizing antibody titers and live virus neutralizing antibody titers were measured in only 4 and 1 of the COVID-19-positive participants, respectively, in the Immunogenicity Analysis Set. Therefore, it is difficult to perform a meaningful analysis of the relationship between the protective effect against COVID-19 and neutralizing antibody titers in this size of subgroup. However, the relationship between the protective effect against COVID-19 and neutralizing antibody titers will be analyzed when sufficient amount of data become available.

[2] Cellular immunity

The applicant's explanation:
The evaluation of S-protein-specific T-cell response by IFN-γ ELISpot in the SDSD + LDSD Seronegative Immunogenicity Analysis Set showed that the geometric mean [2-sided 95% CI] IFN-γ spot forming cell count (SFC) was 607.7 [518.8, 711.9] SFC/10^6 PBMCs at 28 days after the first dose of Vaxzevria and 421.6 [344.5, 516.0] SFC/10^6 PBMCs at 28 days after the second dose of Vaxzevria. This indicates that T-cell response was induced after the first dose but was not enhanced by the second dose.

The evaluation of S-protein-specific T-cell response by intracellular cytokine staining in participants receiving SDSD in Studies COV001 and COV002 revealed an increase in Th1 cytokines (IFN-γ, IL-2, and TNF-α) with almost no increase in Th2 cytokines (IL-4 and IL-13) at 28 days after the first and second doses. This indicates an induction of S-protein-specific Th1 polarized immune response after Vaxzevria vaccination.

PMDA's conclusion:

Further data collection and evaluation are needed to elucidate the relationship between the protective effect of Vaxzevria against COVID-19 and neutralizing antibody titers. Nevertheless, immune response was observed after the administration of Vaxzevria SD in all subgroups regardless of participant characteristics, and a further increase in neutralizing antibody titers was observed after the second dose.

Neutralizing antibody titers after the second dose of Vaxzevria appeared to be higher in the LDSD analysis set than in the SDSD analysis set, but neutralizing antibody titers of the 2 analysis sets were similar after adjusting for the dose interval (Section 7.R.2.2.1.3). Therefore, combining the LDSD and SDSD populations into a single group to evaluate the efficacy and safety of Vaxzevria for the present application posed no problem.

However, according to the results by country, the neutralizing antibody titers were higher in the subgroup of South Africa than in the other subgroups despite that the majority of participants in the subgroup were vaccinated at the interval of 4 weeks (93.7% of participants in the Vaxzevria group were vaccinated at the interval of ≤5 weeks). To investigate this finding, the collection of data including those on the effect of variants (see Section 7.R.2.4) should be continued in the post-marketing setting.

7.R.2.2.1.3 Effects of dose interval on efficacy

The applicant's explanation about the effects of dose interval on efficacy:
At the beginning of this clinical development program, Vaxzevria was planned to be developed for a single-dose vaccination. However, after the review of immunogenicity data from Study COV001 showing increased immunogenicity post second dose (see Section 7.R.6.1), the implementation of more extensive evaluation of the 2-dose vaccination was decided after the start of studies. Meanwhile, despite increased production scale of the study vaccine, the rapid expansion of the clinical development program caused a delay in the supply of study vaccine for the second dose in all 4 studies, mainly affecting the UK studies (Studies COV001 and COV002). Although such delay resulted in dose intervals varying from 3 to 28 weeks, no true difference was presumed between the vaccination regimens. Thus, the populations with different dose intervals were handled as a single population for the analysis.

Table 34 shows efficacy (VE) by dose interval in the Seronegative for Efficacy Analysis Set at the primary analysis (DCO2). In participants with a dose interval of ≥4 weeks, there was a trend toward higher VE with longer dose intervals in both SDSD + LDSD Seronegative for Efficacy Analysis Set and SDSD Seronegative for Efficacy Analysis Set.

Table 34 VE against First SARS-CoV-2 Virologically Confirmed Symptomatic COVID-19 Occurring ≥15 Days Post Second Dose by Dose Interval in the Pooled Analysis (DCO2)

Dose interval	Number of COVID-19 cases		VE (%)	Two-sided 95% CI[a)]
	Vaxzevria, n/N (%)	Control, n/N (%)		
SDSD + LDSD Seronegative for Efficacy Analysis Set				
<4 weeks	1/206 (0.49)	3/203 (1.48)	66.56	[-221.83, 96.53]
≥4 weeks to <8 weeks	47/4312 (1.09)	90/4200 (2.14)	50.48	[29.56, 65.19]
≥8 weeks to ≤12 weeks	23/2308 (1.00)	92/2348 (3.92)	74.97	[60.48, 84.14]
>12 weeks	13/1771 (0.73)	63/1830 (3.44)	78.91	[61.68, 88.39]
SDSD Seronegative for Efficacy Analysis Set				
<4 weeks	1/206 (0.49)	3/203 (1.48)	66.56	[-221.83, 96.53]
≥4 weeks to <8 weeks	47/4294 (1.09)	90/4183 (2.15)	50.48	[29.55, 65.19]
≥8 weeks to ≤12 weeks	18/1555 (1.16)	66/1580 (4.18)	72.64	[53.95, 83.75]
>12 weeks	8/1146 (0.7)	38/1213 (3.13)	77.62	[51.98, 89.57]
LDSD Seronegative for Efficacy Analysis Set				
<4 weeks	0/0	0/0	NA	NA
≥4 weeks to <8 weeks	0/18	0/17	NC	NC
≥8 weeks to ≤12 weeks	5/753 (0.66)	26/768 (3.39)	80.80	[50.05, 92.62]
>12 weeks	5/625 (0.80)	25/617 (4.05)	80.78	[49.86, 92.63]

N = number of participants analyzed; n = number of participants with events; NA = not applicable; NC = not calculated

a) Poisson regression with vaccine group as factor and the log of the follow-up period as an offset variable

Table 35 shows immunogenicity data (neutralizing antibody titers) by dose interval. As with VE, there was a trend toward higher neutralizing antibody titers after the second dose with longer dose intervals in participants with a dose interval of ≥4 weeks.

Table 35 Neutralizing Antibody Titers against SARS-CoV-2 after the Second Dose in the Pooled Analysis (Neutralizing Antibody Assay Using Pseudovirus) (Immunogenicity Analysis Set, DCO2)

Dose interval		SDSD + LDSD		SDSD	LDSD
		Vaxzevria	Control	Vaxzevria	Vaxzevria
	N	2079	1536	1706	373
<4 weeks	n/N_{sub}	17/32	20/32	17/32	NA
	GMT	**326.744**	**24.389**	**325.744**	NA
	[2-sided 95% CI]	[207.22, 515.22]	[16.10, 36.94]	[207.22, 515.22]	NA
≥4 weeks <8 weeks	n/N_{sub}	359/818	369/674	356/815	3/3
	GMT	**131.693**	**21.184**	**130.936**	**261.046**
	[2-sided 95% CI]	[115.98, 149.54]	[20.27, 22.13]	[115.22, 148.79]	[45.31, 1503.97]
≥8 weeks <12 weeks	n/N_{sub}	274/775	170/557	182/587	92/188
	GMT	**213.815**	**21.674**	**215.953**	**209.647**
	[2-sided 95% CI]	[189.94, 240.69]	[20.23, 23.22]	[187.10, 249.25]	[169.37, 259.50]
>12 weeks	n/N_{sub}	184/454	124/273	121/272	63/182
	GMT	**247.973**	**23.035**	**272.323**	**207.145**
	[2-sided 95% CI]	[209.22, 293.90]	[20.57, 25.80]	[219.92, 337.22]	[156.34, 274.47]

N = number of participants per subgroup; n = number of participants evaluated; NA = not applicable

PMDA's conclusion:

In the pooled analysis, the dose intervals varied among vaccinated participants due to various constraints in each clinical study (the Vaxzevria group, 3 to 28 weeks). The analysis, however, was performed by handling participants with different dose intervals as a single population, and the results showed a trend toward higher VE and neutralizing antibody titers with longer dose intervals. In normal circumstances, the applicant would have been required to investigate more appropriate dose intervals. However, there was a compelling need to supply SARS-CoV-2 vaccines promptly in the real situation, and the results of the subgroup analyses by country or age were consistent with the results in the overall population. Thus, the efficacy of Vaxzevria can be evaluated with due consideration of the effects of different dose intervals.

The dosing regimen of Vaxzevria including the dose interval is discussed in Section 7.R.6.

7.R.2.2.2 Efficacy in Japanese participants

The applicant's explanation:

In FVS-1 (the primary analysis set) and FVS-2 (the additional analysis set) in Japanese Study D8111C00002, 100% of the anti-S protein antibody response rate (percentage of participants with at least a 4-fold increase in antibody titers from baseline) was achieved at 56 days after the first dose in both cohorts of the Vaxzevria group, similarly to the results in non-Japanese participants after 2 doses of Vaxzevria SD in the pooled analysis (≥99%; 100% in participants aged ≥65 years). On the other hand, the pseudovirus neutralizing antibody response rate to SARS-CoV-2 was lower in Japanese participants in FVS-1 than in non-Japanese participants in the pooled analysis (66.1% vs. 79.1%). However, all Japanese participants in Japanese Study D8111C00002 received 2 doses at a 4-week interval equally, while non-Japanese participants included in the pooled analysis received 2 doses at a longer interval. This may have caused a lower neutralizing antibody response rate in Japanese participants (see Section 7.R.2.2.1.3).

The GMT [2-sided 95% CI] of the pseudovirus neutralizing antibody titers of Japanese participants at 28 days after the second dose was 103.0 [78.9, 134.4] in FVS-1 (the primary analysis set) and 98.0 [82.4, 116.5] in FVS-2 (the additional analysis set). On the other hand, in the primary analysis (DCO2) of the pooled analysis, the GMT [2-sided 95% CI] of the pseudovirus neutralizing antibody titers at 28 days after the second dose was 130.936 [115.22, 148.79] in participants receiving 2 SD doses of Vaxzevria at a ≥4- to <8-week interval in the SDSD Immunogenicity Analysis Set. This value is higher than that in the Japanese Study D8111C00002. However, the pseudovirus neutralizing antibody titers in non-Japanese participants differed by region. In the subgroup with a dose interval of ≥4 to <8 weeks, the GMT [2-sided 95% CI] of the pseudovirus neutralizing antibody titer at 28 days after the second dose of Vaxzevria was 97.434 [79.81, 118.95] in UK and 110.964 [91.06, 135.22] in Brazil, but 268.614 [211.63, 340.94] in South Africa. The values observed in UK and Brazil were similar to those observed in the Japanese Study D8111C00002, suggesting that the difference in neutralizing antibody titers between Japanese and non-Japanese populations may be due to the higher neutralizing antibody titers observed in South Africa.

Based on these results, there is no clear difference in immunogenicity induced by 2 doses of Vaxzevria SD between Japanese and non-Japanese participants.

PMDA requested that the applicant explain the following points and discuss again whether the immunogenicity after Vaxzevria vaccination in the Japanese population was similar to that observed in non-Japanese populations.

The applicant provided the following explanation:

[1] Reasons for lower GMT in Cohort C (18 to 55 years old) than in Cohort D (≥56 years old) in FVS-1 of Japanese Study D8111C00002

In FVS-1, the GMT [2-sided 95% CI] of the pseudovirus neutralizing antibody titers at 28 days after the second dose of Vaxzevria in Cohort C was 83.7 [57.9, 120.9], which was lower than that in Cohort D (122.8 [83.3, 180.9]) (see Table 16 in Section 7.1.1). This data variation may have been due to the division of participants

into multiple small cohorts. In FVS-2, the GMT [2-sided 95% CI] of the pseudovirus neutralizing antibody titers at 28 days after the second dose in Cohorts C and D was 107.3 [84.2, 136.7] and 90.0 [70.1, 115.6], respectively, showing a numerically lower antibody titer in the elderly than in the non-elderly. In FVS-2, the GMT [2-sided 95% CI] in the subcohorts D1 (56 to 69 years old) and D2 (≥70 years old) was 101.5 [74.3, 138.5] and 70.2 [45.6, 108.1], respectively, showing a trend toward decreased antibody titers with increasing age. However, these differences in GMTs were not considered to be clinically significant because of substantial variability in individual titers and the overlapped 2-sided 95% CIs between the cohorts.

[2] Participants with no increase in neutralizing antibody titers after the second dose (booster effect)

Based on the results in FVS-1 (81 participants), GMTs at 28 days after the second dose slightly increased from GMTs after the first dose for both anti-S and neutralizing antibody titers, particularly with a very slight increase in Cohort C (see Table 16 in Section 7.1.1). However, in FVS-2 (234 participants, including 153 additional participants), including Cohort C, the degree of increase in GMTs for both anti-S and neutralizing antibody titers were similar to that observed in the pooled analysis.

In FVS-2 in Japanese Study D8111C00002,[25)] 26.6% (41/154) of participants showed no booster effect on the pseudovirus neutralizing antibody titers after the second dose of Vaxzevria. In the pooled analysis (participants who were seronegative at baseline), 17.1% (102/597) of participants showed no booster effect. In both Japanese Study D8111C00002 and the pooled analysis, the proportion of participants without a booster effect was lower in the elderly (≥56 years old) than in the non-elderly (18 to 55 years old), with no clear difference between men and women, and with no difference between different BMIs or dose intervals.

The analytical method used to determine the pseudovirus neutralizing antibody titers was properly validated and recognized as a sufficiently accurate cellular assay, but measured values varied relatively largely (CV: 34.7% to 56.7%). This suggested that some participants had no booster effect after the second dose of Vaxzevria. In fact, of 5 participants in the pooled analysis who did not demonstrate a booster effect on the pseudovirus neutralizing antibody titers and had live virus neutralizing antibody titer data, 4 participants had increased live virus neutralizing antibody titer.

[3] Appropriateness of evaluating participants enrolled before and after study interruption as a single group

In Japanese Study D8111C00002, the FVS-1-based analysis and the FVS-2-based analysis showed different immunogenicity results, but participant characteristics, compared by cohort, were similar between 81 FVS-1 participants and 153 non-FVS-1 participants. In general, immune responses are inherently variable due to diverse host and environmental factors, even among participants with similar baseline characteristics. Of all 5 study sites, only 2 study sites included FVS-1 participants, 1 of which did not include additional participants. However, the study vaccine and samples at all study sites were handled in accordance with their own written procedures, with no critical protocol deviations. Meanwhile, anti-S protein antibody and pseudovirus neutralizing antibody

25) The analysis was performed on the 174 participants in the Vaxzevria group in FVS-2, excluding 20 participants whose neutralizing antibody titer was above LLoQ but did not meet the specificity criterion (i.e., at least 3 times the neutralizing antibody titers in participants receiving the negative controls).

were determined at the same laboratory.

Based on the above, the differences in immunogenicity results of Vaxzevria between FVS-1 and FVS-2 were most likely attributable to random heterogeneity of the sample population and variation in measured values. A maximal possible sample size will allow more appropriate interpretation of evaluation.

[4] Participants with neutralizing antibody titers <LLoQ after both the first and second doses of Vaxzevria SD

Table 36 shows the proportion of participants receiving 2 doses of Vaxzevria SD who had pseudovirus neutralizing antibody titers below LLoQ after both the first and second doses in Japanese Study D8111C00002 or in the primary analysis (DCO2) of the pooled analysis. Pseudovirus neutralizing antibody titers were determined at the same laboratory in Japanese Study D8111C00002 and all studies included in the pooled analysis.

Table 36 Proportion of Participants Receiving 2 Doses of Vaxzevria SD Who Had Pseudovirus Neutralizing Antibody Titers below LLoQ after Both the First and Second Doses in Japanese Study D8111C00002 or the Primary Analysis (DCO2) of the Pooled Analysis

		Japanese Study D8111C00002 (FVS-2 [a])		Primary analysis (DCO2) of the pooled analysis (SDSD Seronegative for Efficacy Analysis Set)	
		No response[b]		No response[b]	
		n/N	%	n/N	%
All		32/154	20.8	64/597	10.7
Age	18-55 years	12/73	16.4	23/428	5.4
	≥56 years	20/81	24.7	41/169	24.3
	56-69 years	12/54	22.2	33/117	28.2
	≥70 years	8/27	29.6	8/52	15.4
Sex	Male	25/99	25.3	33/308	10.7
	Female	7/55	12.7	31/289	10.7
BMI	<30 kg/m^2	30/148	20.3	46/496	9.3
	≥30 kg/m^2	2/6	33.3	18/99	18.2
Dose interval	4 weeks (±2 days)	32/154	20.8	12/123	9.8
	<6 weeks	32/154	20.8	47/283	16.6
	6-8 weeks	ND	NC	7/110	6.4
	9-11 weeks	ND	NC	4/83	4.8
	≥12 weeks	ND	NC	6/121	5.0

N = number of participants per subgroup; n = number of participants with neutralizing antibody titers below LLoQ; ND = no data; NC = not calculated

a) Of the 174 participants in the Vaxzevria group in FVS-2, 20 participants were excluded who had a neutralizing antibody titer above LLoQ (40) but <3 times that in participants receiving the negative control.

b) No response: neutralizing antibody titers below LLoQ after both the first and second doses of Vaxzevria.

In both Japanese Study D8111C00002 and the pooled analysis, the proportion of participants with pseudovirus neutralizing antibody titers below LLoQ was higher in the elderly (≥56 years old) than in the non-elderly (18 to 55 years old). In the pooled analysis, the proportion of participants with the pseudovirus neutralizing antibody titers below LLoQ tended to decrease with longer dose interval. However, the dose interval was generally shorter in the elderly in the pooled analysis, which suggested possible confounding between the age category and dose interval (see Section 7.R.2.2.1.3). Thus, no different tendency was observed between the Japanese and non-Japanese populations.

Based on the above results, the immunogenicity of Vaxzevria observed in each cohort in Japanese Study D8111C00002 was similar to that observed in the pooled analysis, suggesting similar efficacy in the Japanese population.

PMDA's conclusion:
The observed variability in the measurements of neutralizing antibody titers poses some difficulty in the interpretation of the results from the limited number of Japanese participants. However, the neutralizing antibody titers after the second dose of Vaxzevria in Japanese Study D8111C00002 were not largely different from those after the second dose in the subgroups of UK and Brazil with the dose interval of 4 to 8 weeks in the pooled analysis. In addition, the neutralizing antibody titers increased in the Japanese elderly as did in the non-elderly population. The immune responses measured by anti-S protein antibody in Japanese participants were similar to those in non-Japanese participants. Thus, immune response after the administration of Vaxzevria did not tend to differ largely between the Japanese and the non-Japanese populations.

The pooled analysis suggested no marked effects of country or race on VE and immunogenicity results, except for the results of SARS-CoV-2 variants (lineage B.1.351) [see Section 7.R.2.4]. Based on this finding, together with the above ones, Vaxzevria is expected to have efficacy in Japanese population of any age ≥18 years.

7.R.2.2.3 Efficacy in elderly people

Table 30 in Section 7.R.2.2.1.1 shows the results of the subgroup analysis by age in the pooled analysis.

The applicant' explanation about the efficacy in the elderly:
At the primary analysis (DCO2), adults aged ≥65 years accounted for only 8.2% (703 participants in the Vaxzevria group and 680 participants in the control group) of the primary efficacy set (SDSD + LDSD Seronegative for Efficacy Analysis Set) in the pooled analysis. All participants aged ≥65 years received the SDSD regimen, and the majority (89.6% of participants in the Vaxzevria group and 87.8% of participants in the control group) had a dose interval of <6 weeks. The follow-up period after the first dose (mean ± SD) was 82.9 ± 21.5 days, and the follow-up on and after 15 days post second dose (mean ± SD) was 34.9 ± 20.9 days.

In adults aged ≥65 years in the SDSD + LDSD Seronegative for Efficacy Analysis Set, COVID-19 occurred ≥15 days after the second dose in 4 of 703 participants (0.57%) in the Vaxzevria group and 8 of 680 participants (1.18%) in the control group. In adults aged ≥65 years in the First SD Seronegative for Efficacy Analysis Set, COVID-19 occurred ≥22 days after the first SD dose in 6 of 945 participants (0.63%) in the Vaxzevria group and 13 of 896 participants (1.45%) in the control group; among them, 0 (Vaxzevria group) and 2 (control group) participants were hospitalized for COVID-19 and no participants had severe COVID-19 in either group.

As described above, only a small number of events qualified for VE assessment occurred in the elderly aged ≥65 years, but the results in the age group were consistent with those in the overall population.

Table 37 shows changes in neutralizing antibody titers by age in the pooled analysis. Considering the difference in dose interval as a confounder (see Section 7.R.2.2.1.3), Vaxzevria induced neutralizing antibodies in all age groups. The neutralizing antibody titer tended to be lower in the elderly than in the non-elderly, but the clinical

significance of this finding is unknown at present.

Table 37 Changes in Neutralizing Antibody Titers against SARS-CoV-2 after 2 Doses of Vaxzevria SD in the Pooled Analysis by Age Group (Neutralizing Antibody Assay Using Pseudovirus) (Immunogenicity Analysis Set, Seronegative, DCO2)

		18-55 years old		56-69 years old		≥70 years old	
		Vaxzevria N = 1287	Control N = 962	Vaxzevria N = 250	Control N = 222	Vaxzevria N = 169	Control N = 131
Baseline	n	549	391	133	127	56	58
	GMT [2-sided 95% CI]	20.710 [20.13, 21.31]	20.375 [19.95, 20.81]	20.0 [NE, NE]	20.0 [NE, NE]	20.0 [NE, NE]	20.0 [NE, NE]
28 days after the first dose	n	476	380	122	122	54	54
	GMT [2-sided 95% CI]	74.268 [65.84, 83.78]	21.172 [20.27, 22.12]	36.568 [30.66, 43.61]	20.963 [19.51, 22.52]	36.037 [27.12, 47.89]	20.0 [NE, NE]
28 days after the second dose	n	493	375	128	126	55	58
	GMT [2-sided 95% CI]	221.642 [200.80, 244.65]	22.505 [21.20, 23.90]	85.511 [69.72, 104.89]	20.450 [19.57, 21.37]	109.684 [81.14, 148.26]	20.0 [NE, NE]

N = number of participants per subgroup; n = number of participants evaluated; NE = not evaluable

The results of neutralizing antibody titers in the Japanese elderly are not substantially different from those in the non-elderly population (see Section 7.R.2.2.2).

PMDA's conclusion:
Due to the limited number of elderly participants included in the pooled analysis, the efficacy of Vaxzevria in the elderly subgroup is not clear. Elderly participants showed lower neutralizing antibody titers after Vaxzevria vaccination than non-elderly participants. However, most elderly participants in the pooled analysis received Vaxzevria at an interval of <6 weeks, and the neutralizing antibody titer tended to increase with the increasing dose interval (see Section 7.R.2.2.1.3). Therefore, it is reasonable to consider that neutralizing antibody titers increase after Vaxzevria vaccination in the elderly population as did in the non-elderly population. Further, at present, there is no evidence suggesting inconsistency in efficacy between the elderly and non-elderly populations. Thus, Vaxzevria is expected to have efficacy in all age groups ≥18 years, including the elderly.

PMDA will draw the final conclusion on the efficacy of Vaxzevria in the elderly based on comments raised at the expert discussion and preliminary results from the ongoing US Study D8110C00001.

7.R.2.3 Protective effect against severe COVID-19

The applicant's explanation about the protective effect of Vaxzevria against severe COVID-19:
Prior to the evaluation of the protective effect of Vaxzevria against severe COVID-19, severe cases were defined as shown in Table 38-2 based on WHO definition of severe cases (Table 38-1, *Lancet Infect Dis.* 2020; 20: e192-7), and the occurrence was reviewed. In the UK studies (Studies COV001 and COV002), ICU admission was defined as an endpoint in the protocol. For the pooled analysis, however, ICU admission was redefined to standardize the medical practice that differs between regions among the studies. Cases of ICU admission were reclassified into WHO severity categories requiring mechanical ventilation.

Table 38-1 WHO Severity Criteria

Patient status	Description of severity	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory, mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized, moderate disease	Hospitalized; no oxygen therapy (If hospitalized for isolation only, classify as ambulatory)	4
	Hospitalized; oxygen (by mask or nasal cannula)	5
Hospitalized, severe diseases	Hospitalized; oxygen (by non-invasive ventilation or high flow)	6
	Intubation and mechanical ventilation (pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200)	7
	Mechanical ventilation (pO_2/FiO_2 <150 [SpO_2/FiO_2 <200] or vasopressors)	8
	Mechanical ventilation (pO_2/FiO_2 <150) and vasopressors, dialysis, or ECMO	9
Dead	Death	10

Table 38-2 Definitions of Severe Cases

Case	Definition
Hospitalization related to COVID-19	WHO severity score ≥4
Severe COVID-19	WHO severity score ≥6
ICU admission related to COVID-19	WHO severity score ≥7
Death related to COVID-19	WHO severity score 10

Table 39 shows the efficacy against COVID-19-related hospitalization and severe COVID-19 in the SDSD + LDSD Seronegative for Efficacy Analysis Set at the primary analysis (DCO2). Although the number of accrued events was small, the efficacy of Vaxzevria showed a consistent trend. Other analysis sets also showed a consistent trend in the efficacy of Vaxzevria.

Table 39 Efficacy against COVID-19-Related Hospitalizations and Severe COVID-19 (DCO2)

Analysis set	Follow-up period	Hospitalization related to COVID-19					Severe COVID-19				
		Vaxzevria		Control		VE% [97.5% CI][a)]	Vaxzevria		Control		VE% [97.5% CI][a)]
		N	n (%)	N	n (%)		N	n (%)	N	n (%)	
SDSD + LDSD, seronegative	≥15 days after the second dose	8597	0	8581	9 (0.10)	100 [50.19, NE]	8597	0	8581	2 (0.02)	100 [-432.68, NE]
SDSD, seronegative	≥15 days after the second dose	7201	0	7179	8 (0.11)	100 [42.58, NE]	7201	0	7179	1 (0.01)	100 [-3742.53, NE]
Any dose	After the first dose	11794	2 [b)] (0.02)	11776	22 (0.19)	90.92 [63.06, 98.97]	11794	0	11776	3 (0.03)	100 [-143.64, NE]

NE: Not Evaluable

a) Stratified Poisson regression with vaccine group as factor, and study identifier and age at screening (18 to 55, 56 to 69, ≥70 years) as strata factors

b) One participant developed COVID-19 one day after the first dose, and the other 10 days after the first dose.

PMDA's view:

Only a very limited number of patients experienced COVID-19-related hospitalization or severe COVID-19, and therefore the efficacy of Vaxzevria against COVID-19-related hospitalization and severe COVID-19 is not clear at present. Nevertheless, there are no data casting a large doubt on the protective effect of Vaxzevria against severe COVID-19. Once new findings become available, appropriate measures, such as discussion on the necessity of information provision, should be taken as necessary.

7.R.2.4 Efficacy against variants

PMDA requested that the applicant explain the efficacy of Vaxzevria against new SARS-CoV-2 variants (e.g., lineage B.1.1.7, lineage B.1.351, lineage B.1.1.248, lineage B.1.429) that have been reported in UK, South Africa, Brazil, US, Japan, etc., as well as how the efficacy of Vaxzevria should be evaluated for future new

variants.

The applicant's explanation:
In a preliminary assessment conducted in cooperation with the University of Oxford and the University of the Witwatersrand, the efficacy and immunogenicity of Vaxzevria against lineage B.1.1.7 were evaluated based on the data from Study COV002 (as of [redacted], 20[redacted], unlocked data) (*Lancet.* 2021; DOI: https://doi.org/10.1016/S0140-6736(21)00628-0). Of the events included in the primary efficacy analysis with available viral nucleic acid sequences, 34 events (28.3%) were caused by the B.1.1.7 variant and 86 events (71.7%) by non-B.1.1.7 variants. The VE of Vaxzevria was similar between the B.1.1.7 variant (74.6% [2-sided 95% CI: 41.6, 88.9]) and non-B-1.1.7 variants (84.1% [2-sided 95% CI: 70.7, 91.4]). In contrast, the neutralizing antibody titer against the B.1.1.7 variant was 1/9 of that against Victoria strain[26)] when measured by the live virus neutralizing antibody assay using sera from participants receiving Vaxzevria (GMT [2-sided 95% CI]: 58 [44, 77] against the B.1.1.7 variant; 517 [424, 631] against Victoria strain).

In the preliminary assessment conducted in cooperation with the University of Oxford and the University of the Witwatersrand, the efficacy and immunogenicity of Vaxzevria against lineage B.1.351 were evaluated based on the data from Study COV005 (as of [redacted], 20[redacted], unlocked data) (*N Engl J Med.* 2021; DOI: 10.1056/NEJMoa2102214). In the primary analysis, COVID-19 occurred in 2.5% (19 of 750 participants) in the Vaxzevria group and 3.2% (23 of 717 participants) in the placebo group, and VE was 21.9% (2-sided 95% CI: -49.9, 59.8). Of 42 participants who developed COVID-19, 39 had lineage B.1.351 with available viral nucleic acid sequences. The VE of Vaxzevria against the B.1.351 variant was 10.4% (2-sided 95% CI: -76.8, 54.8). In the live virus neutralizing antibody assay using sera from participants receiving Vaxzevria, 12 samples showed the neutralizing activity against the B.1.1 variant.[27)] Of the 12 samples, however, 7 (58%) showed no neutralizing activity against the B.1.351 variant, and the remaining 5 showed a 4.1- to 31.5-fold decrease in activity against the variant. Thus, its protective effect against mild to moderate COVID-19 caused by the B.1.351 variant has not been established, but Vaxzevria may have a protective effect against severe COVID-19 caused by the B.1.351 variant, as suggested by cross-reactivity of T-cell epitopes and data of other vaccines under development. The applicant is currently discussing how to obtain data on the efficacy against hospitalization and severe COVID-19 from the regions where relevant variants are prevalent.

Lineage P.1 (lineage B.1.1.248) is another isolated strain planned to be analyzed for phenotype identification at the earliest possible time. B.1.429 variant accounted for 10% to 20% of circulating SARS-CoV-2 strains in US as of February 2021 (https://outbreak.info/situation-reports?pango=B.1.429&loc=USA&loc=USA_US-CA&selected=USA_US-CA [last accessed on April 6, 2021]). Some efficacy data on lineage B.1.429 may become available from Study D8110C00001, which is ongoing in US, Chile, and Peru.

26) Australia/VIC01/2020 strain: This virus strain was isolated from a nasopharyngeal swab of a patient who developed COVID-19 soon after arriving at Melbourne from Wuhan, China in January 2020. S247R mutation is present in the S protein, but the infectivity is assumed to be equivalent to that of the virus strain that became epidemic in the early stage.
27) B.1.1 D614G variant isolated from samples obtained during the first wave of COVID-19 epidemic in South Africa.

Neutralizing antibodies against the B.1.1.7, B.1.1.248, and B.1.351 variants were measured using sera from participants receiving 2 doses of Vaxzevria in Study COV001 (see Section 7.1.2). The results are shown in Section 3.R.2.

The applicant prepared the following plan for comprehensive virological clinical investigation, and will continue to conduct the investigation.

- For the viral genomes that have been amplified and sequenced from SARS-CoV-2 positive samples collected from COVID-19 patients in the clinical studies of Vaxzevria, the frequency of simultaneous amino acid mutations is determined and lineages are assigned.
- For phenotyping, the frequency and geographic distribution of concurrently circulating viral strains are investigated based on the thresholds specified in global and regional surveys to identify variants of concern.
- The neutralizing activity against the variant viruses of concern in sera from recipients of Vaxzevria is evaluated by a neutralization activity assay using quality-assured pseudovirus and live viruses, to provide an indicator of the protective effect against variants.
- In each study, the clinical efficacy of Vaxzevria against COVID-19 caused by variants of concern (VOC) versus non-VOC strains is evaluated by geographic region and in overall population.

In addition, the development of vaccines for variants is in progress as a risk mitigation measure.

PMDA's conclusion:

In light of the applicant's explanation, Vaxzevria is expected to have a certain level of efficacy against the viruses, except for the B.1.351 variant, that were dominant when the studies included in the pooled analysis were underway. Further data on the benefits of Vaxzevria against the B.1.351 variant should be collected. In the post-marking setting, the applicant should continue to investigate and collect data on the induction of neutralizing activity of Vaxzevria and the efficacy against reported variants other than the above and future emerging variants. When new findings become available, the applicant should disseminate the findings as needed and take other appropriate actions.

7.R.3 Safety

7.R.3.1 Safety profile

Injection-site or systemic AEs were observed in many participants included in the pooled analysis and Japanese Study D8111C00002, but most of them were mild or moderate in severity and reversible, and there were no major differences in the safety profiles between Japan and non-Japanese participants. Given these, and based on the occurrence of other AEs, including the incidences by age, etc., PMDA concluded that the safety profile indicates no significant concerns that will affect the decision on the approval of Vaxzevria, as a result of the following review.

Because of the limited safety follow-up period (mean ± standard deviation [SD]) of 68.9 ± 35.74 days for the Vaxzevria group of the Dose 1 SD Safety Analysis Set in the pooled analysis, the long-term safety data of Vaxzevria should be continuously collected in the post-marketing setting.

Adverse events of special interest and the safety in special populations are further reviewed in Sections 7.R.3.2 and later.

7.R.3.1.1 Adverse events in clinical studies

[1] Pooled analysis

The applicant's explanation about the occurrence of AEs in the pooled analysis:
Note that, in the following explanations, "participants in the Dose 1 SD for Safety Analysis Set whose diaries were collected" are defined as participants evaluated for Dose 1 SD solicited AEs.

Solicited AEs and unsolicited AEs in the Dose 1 SD for Safety Analysis Set in the pooled analysis were evaluated, as an analysis related to the proposed dosage and administration. Tables 40-1, 40-2 and 40-3 summarize solicited AEs occurring within 7 days after the study vaccination (after the first or second dose, irrespective of the dose number) in participants evaluated for Dose 1 SD solicited AEs.

Table 40-1 Summary of Solicited Adverse Events Occurring within 7 Days after Vaccination Regardless of Dose Number in Pooled Analysis (Participants Evaluated for Dose 1 SD Solicited AEs, DCO2)

Study vaccine	Vaxzevria	Control			
		All controls combined	Meningococcal vaccine 2-dose	Meningococcal vaccine + placebo	Placebo 2-dose
Number of participants	2725	2537	1514	100	959
Solicited AEs	2332 (85.6)	1835 (71.3)	1280 (84.5)	81 (81.0)	474 (49.4)
Solicited local AEs	2002 (73.5)	1224 (48.3)	968 (63.9)	60 (60.0)	216 (22.5)
Grade ≥3	52 (1.9)	19 (0.7)	6 (0.4)	1 (1.0)	12 (1.3)
Solicited systemic AEs	1991 (73.1)	1548 (60.2)	1066 (70.4)	65 (65.0)	417 (43.5)
Grade ≥3	229 (8.4)	67 (2.6)	26 (1.7)	1 (1.0)	40 (4.2)

( ) Figures in parentheses indicate percentage (%).
For the definition of Grade ≥3, see Section 11.2, Tables 56-1 to 3.

Table 40-2 Summary of Solicited Adverse Events Occurring within 7 Days after the First Dose in Pooled Analysis (Participants Evaluated for Dose 1 SD Solicited AEs, DCO2)

Study vaccine	Vaxzevria	Control			
		All controls combined	Meningococcal vaccine 2-dose	Meningococcal vaccine + placebo	Placebo 2-dose
Number of participants	2664	2503	1493	100	910
Solicited AEs	2199 (82.5)	1642 (65.6)	1198 (80.2)	78 (78.0)	366 (40.2)
Solicited local AEs	1845 (69.3)	1094 (43.7)	871 (58.3)	57 (57.0)	166 (18.2)
Grade ≥3	38 (1.4)	14 (0.6)	4 (0.3)	1 (1.0)	9 (1.0)
Solicited systemic AEs	1851 (69.5)	1342 (53.6)	968 (64.8)	62 (62.0)	312 (34.3)
Grade ≥3	197 (7.4)	41 (1.6)	18 (1.2)	1 (1.0)	22 (2.4)

( ) Figures in parentheses indicate percentage (%).
For the definition of Grade ≥3, see Section 11.2, Tables 56-1 to 3.

Table 40-3 Summary of Solicited Adverse Events Occurring within 7 Days after the Second Dose in Pooled Analysis (Participants Evaluated for Dose 1 SD Solicited AEs, DCO2)

Study vaccine	Vaxzevria	Control			
		All controls combined	Meningococcal vaccine 2-dose	Meningococcal vaccine + placebo	Placebo 2-dose
Number of participants	1926	1799	825	70	904
Solicited AEs	1177 (61.1)	847 (47.1)	541 (65.6)	27 (38.6)	279 (30.9)
Solicited local AEs	886 (46.0)	498 (27.7)	375 (45.5)	13 (18.6)	110 (12.2)
Grade ≥3	18 (0.9)	7 (0.4)	3 (0.4)	0	4 (0.4)
Solicited systemic AEs	855 (44.4)	648 (36.0)	387 (46.9)	18 (25.7)	243 (26.9)
Grade ≥3	40 (2.1)	32 (1.8)	8 (1.0)	0	24 (2.7)

( ) Figures in parentheses indicate percentage (%).

For the definition of Grade ≥3, see Tables 56-1 to 3 in Section 11.2.

The occurrence of each solicited local and systemic AE is shown in Table 26 in Section 7.4. In the Vaxzevria group, the major solicited local AEs occurring within 7 days after the first or second dose were tenderness (1,739 of 2,725 participants, 63.8%) and injection site pain (957 of 1,762 participants, 54.3%). Other solicited local AEs with an incidence of ≥10% were feeling hot (315 of 1,762 participants, 17.9%), itching (356 of 2,725 participants, 13.1%), and contusion (172 of 963 participants, 17.9%). Major solicited systemic AEs were fatigue (1,445 of 2,725 participants, 53.0%) and headache (1,435 of 2,725 participants, 52.7%). Other solicited systemic AEs with a high incidence were myalgia (1,197 of 2,725 participants, 43.9%), malaise (783 of 1,762 participants, 44.4%), feverishness (591 of 1,762 participants, 33.5%), chills (568 of 1,762 participants, 32.2%), arthralgia (724 of 2,725 participants, 26.6%), nausea (391 of 1,762 participants, 22.2%), and pyrexia (205 of 2,695 participants, 7.6%). The incidence of solicited local and systemic AEs in the Vaxzevria group was lower after the second dose than after the first dose.

As for severity (see Section 11.2), most solicited AEs in the Vaxzevria group were mild or moderate. Table 41 shows Grade ≥3 solicited AEs occurring within 7 days after the first and second doses of the study vaccine. The incidences of Grade ≥3 solicited local or systemic AEs in the Vaxzevria group were generally lower after the second dose than after the first dose.

Table 41 Grade ≥3 Solicited Adverse Events Occurring within 7 Days after the First and Second Doses in Pooled Analysis (Participants Evaluated for Dose 1 SD Solicited AEs, DCO2)

Event term	After the first dose of study vaccine					After the second dose of study vaccine				
		Control					Control			
	Vaxzevria	All controls combined	Meningococcal vaccine 2-dose	Meningococcal vaccine + placebo	Placebo 2-dose	Vaxzevria	All controls combined	Meningococcal vaccine 2-dose	Meningococcal vaccine/placebo	Placebo 2-dose
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Local										
All	38/2656 (1.4)	14/2496 (0.6)	4/1493 (0.3)	1/100 (1.0)	9/903 (1.0)	18/1922 (0.9)	7/1796 (0.4)	3/825 (0.4)	0/70 (0)	4/901 (0.4)
Injection site pain	9/1745 (0.5)	2/1593 (0.1)	2/1493 (0.1)	0/100 (0)	-	0/1011 (0)	1/895 (0.1)	1/825 (0.1)	0/70 (0)	-
Tenderness	25/2655 (0.9)	4/2496 (0.2)	3/1493 (0.2)	0/100 (0)	1/903 (0.1)	14/1920 (0.7)	4/1794 (0.2)	2/825 (0.2)	0/70 (0)	2/899 (0.2)
Redness	2/2623 (0.1)	2/2466 (0.1)	1/1493 (0.1)	1/100 (1.0)	0/873 (0)	0/1877 (0)	1/1744 (0.1)	1/825 (0.1)	0/70 (0)	0/849 (0)
Feeling hot	0/1745 (0)	0/1593 (0)	0/1493 (0)	0/100 (0)	-	0/1011 (0)	0/895 (0)	0/825 (0)	0/70 (0)	-
Itching	8/2655 (0.3)	5/2495 (0.2)	0/1493 (0)	0/100 (0)	5/902 (0.6)	7/1920 (0.4)	1/1794 (0.1)	0/825 (0)	0/70 (0)	1/899 (1.0)
Swelling	2/2622 (0.1)	0/2466 (0)	0/1493 (0)	0/100 (0)	0/873 (0)	0/1876 (0)	0/1745 (0)	0/825 (0)	0/70 (0)	0/850 (0)
Induration	2/1745 (0.1)	0/1593 (0)	0/1493 (0)	0/100 (0)	-	0/1011 (0)	0/895 (0)	0/825 (0)	0/70 (0)	-
Contusion	4/910 (0.4)	4/902 (0.4)	-	-	4/902 (0.4)	4/909 (0.4)	1/899 (0.1)	-	-	1/899 (0.1)
Systemic										
All	197/2664 (7.4)	41/2502 (1.6)	18/1493 (1.2)	1/100 (1.0)	22/909 (2.4)	40/1925 (2.1)	32/1799 (1.8)	8/825 (1.0)	0/70 (0)	24/904 (2.7)
Pyrexia	17/2588 (0.7)	4/2422 (0.2)	0/1476 (0)	0/49 (0)	4/897 (0.4)	2/1873 (0.1)	3/1765 (0.2)	1/813 (0.1)	0/63 (0)	2/889 (0.2)
Feverishness	61/1745 (3.5)	1/1593 (0.1)	1/1493 (0.1)	0/100 (0)	-	2/1011 (0.2)	1/895 (0.1)	1/825 (0.1)	0/70 (0)	-
Chills	61/1745 (3.5)	0/1593 (0)	0/1493 (0)	0/100 (0)	-	2/1011 (0.2)	0/895 (0)	0/825 (0)	0/70 (0)	-
Arthralgia	28/2655 (1.1)	7/2494 (0.3)	3/1493 (0.2)	0/100 (0)	4/901 (0.4)	7/1921 (0.4)	7/1794 (0.4)	0/825 (0)	0/70 (0)	7/899 (0.8)
Myalgia	43/2655 (1.6)	6/2495 (0.2)	1/1493 (0.1)	0/100 (0)	5/902 (0.6)	10/1921 (0.5)	5/1794 (0.3)	0/825 (0)	0/70 (0)	5/899 (0.6)
Fatigue	71/2655 (2.7)	18/2496 (0.7)	9/1493 (0.6)	0/100 (0)	9/903 (1.0)	20/1922 (1.0)	11/1796 (0.6)	3/825 (0.4)	0/70 (0)	8/901 (0.9)
Headache	63/2655 (2.4)	15/2496 (0.6)	6/1493 (0.4)	0/100 (0)	9/903 (1.0)	16/1922 (0.8)	16/1796 (0.9)	2/825 (0.2)	0/70 (0)	14/901 (1.6)
Malaise	62/1745 (3.6)	4/1593 (0.3)	4/1493 (0.3)	0/100 (0)	-	7/1011 (0.7)	3/895 (0.3)	3/825 (0.4)	0/70 (0)	-
Nausea	12/1745 (0.7)	1/1593 (0.1)	0/1493 (0)	1/100 (1.0)	-	3/1011 (0.3)	1/895 (0.1)	1/825 (0.1)	0/70 (0)	-
Vomiting	4/1745 (0.2)	1/1593 (0.1)	0/1493 (0)	1/100 (1.0)	-	2/1011 (0.2)	1/895 (0.1)	1/825 (0.1)	0/70 (0)	-

N = number of participants analyzed; n = number of participants with events

For the definition of Grade ≥3, see Tables 56-1 to 3 in Section 11.2.

The incidences of solicited AEs during 7 days after the first or second dose in the Vaxzevria group were highest at 1 day after vaccination (the day after the vaccination), with the incidences of solicited local and systemic AEs being 63.4% and 60.8%, respectively. The incidence of solicited AEs by preferred term (PT) decreased to ≤5% by 7 days after vaccination in most cases, suggesting a short duration of these events.

The occurrence of unsolicited AEs reported within 28 days after the last dose of study vaccine in the Dose 1 SD for Safety Analysis Set is shown in Tables 27-1 to 3 in Section 7.4. The main unsolicited AEs were consistent with commonly reported events in individuals receiving prophylactic vaccines against infections. The majority of unsolicited AEs were mild or moderate. The incidence of Grade ≥3 unsolicited AEs was as follows:

After the first dose: 1.6% (166 of 10,317 participants) in the Vaxzevria group and 1.1% (116 of 10,141 participants) in the all control groups combined (0.7% [26 of 3,944 participants] in the meningococcal vaccine 2-dose group, 1.6% [81 of 5,209 participants] in the meningococcal vaccine + placebo group, and 0.9% [9 of 988 participants] in the placebo 2-dose group).

After the second dose: 0.6% (66 of 10,317 participants) in the Vaxzevria group and 0.6% (60 of 10,141 participants) in the all control groups combined (0.6% [24 of 3,944 participants] in the meningococcal vaccine 2-dose group, 0.5% [25 of 5,209 participants] in the meningococcal vaccine + placebo group, and 1.1% [11 of 988 participants] in the placebo 2-dose group).

The incidence of Grade ≥3 unsolicited AEs in the Vaxzevria group was generally lower after the second dose than after the first dose.

The incidence of unsolicited AEs occurring during 7 days or ≥8 days after vaccination irrespective of the dose number (first or second) in the Vaxzevria group was 35.5% (24.2% in the control group) and 11.4% (10.9% in the control group), respectively. Most of the commonly reported unsolicited AEs occurred within 7 days after Vaxzevria vaccination.

In the studies included in the pooled analysis, some groups of Studies COV001 and COV002 and all participants of Study COV003 were allowed to take prophylactic acetaminophen (see Sections 7.1.2, 7.2.1, and 7.3.1). In any of the studies, the prophylactic administration was not mandatory and at the participant's discretion. In the available results, the effect of prophylactic acetaminophen was limited, although the incidence of solicited AEs was lower in participants who received prophylactic acetaminophen than in those who did not. In addition, the safety profile of Vaxzevria was considered acceptable without prophylactic acetaminophen. Taking account of the above, there appears to be no need to recommend prophylactic acetaminophen for people who receive Vaxzevria.

[2] Japanese Study D8111C00002

The occurrence of AEs in Japanese Study D8111C00002 is shown in Tables 17, 18-1, and 18-2 in Section 7.1.1.

The applicant's explanation about the safety profile of Vaxzevria in the Japanese population (for the definition of Grades, see Tables 56-1, 56-2, and 56-4 in Section 11.2):

In the Vaxzevria group of Total Vaccinated Analysis Set (TVS), most solicited local AEs after the first or second dose were mild or moderate in severity. Severe (Grade 3) events occurred in 2 participants (injection site pain and tenderness in 1 participant, and tenderness in 1 participant, both after the first dose in Cohort C), and no Grade ≥4 events occurred. In the placebo group, no severe (Grade 3) or worse events were observed. The severity and incidence of solicited local AEs in the Vaxzevria group were generally lower after the second dose than after the first dose. In the Vaxzevria group, the severity and incidence of solicited local AEs were lower in the Subcohort D2 (≥70 years old) than in Cohort C or Subcohort D1.

In the Vaxzevria group of TVS, most solicited systemic AEs after the first or second dose were mild or moderate in severity. Severe (Grade 3) events occurred in 9 participants (pyrexia, chills, myalgia, fatigue, headache, malaise, nausea, and vomiting in 1 participant; chills, fatigue, headache, and malaise in 1 participant; chills, myalgia, fatigue, headache, and malaise in 1 participant; pyrexia in 3 participants; chills in 1 participant; headache in 1 participant, and myalgia in 1 participant; all of the events occurred after the first dose in Cohort C), and no Grade ≥4 events were observed. In the placebo group, no severe (Grade 3) or worse events were

observed. The severity and incidence of solicited systemic AEs in the Vaxzevria group were generally lower after the second dose than after the first dose. Also, in the Vaxzevria group, the severity and incidence of solicited systemic AEs were lower in the Subcohorts D1 and D2, which included participants ≥56 years old, than in Cohort C.

The incidences of solicited local AEs, irrespective of the dose number (first or second), in the Vaxzevria group were as high as 53.6% and 56.8% at 1 day (the day after the vaccination) and 2 days after vaccination, respectively. The incidence of solicited systemic AEs were as high as 47.4% at 1 day after vaccination. The incidence of most solicited local and systemic AEs decreased to <10% by 6 days after vaccination, indicating short durations of these events.

The majority of unsolicited AEs, irrespective of the dose number (first or second), was mild or moderate. Severe unsolicited AEs were observed in 6 participants in the Vaxzevria group (4 participants in Cohort C [fatigue, malaise, tenderness, and myalgia in 1 participant, malaise in 1 participant, headache in 1 participant, and dental caries in 1 participant] and 2 participants in Subcohort D1 [neutrophil count decreased in 1 participant and urticaria in 1 participant]) and 2 participants in the placebo group (2 participants in Subcohort D1 [cervical dysplasia in 1 participant and bronchitis in 1 participant]). Of these, a causal relationship to the study vaccine could not be ruled out for 3 participants (fatigue, malaise, tenderness, and myalgia in 1 participant, malaise in 1 participant, and headache in 1 participant) in Cohort C of the Vaxzevria group and 1 participant (neutrophil count decreased) in Subcohort D1 of the Vaxzevria group. One participant in Subcohort D1 of the Vaxzevria group experienced Grade 3 neutropenia 7 days after the first dose and Grade 2 neutropenia 7 days after the second dose. Both events were transient and the levels returned to the reference range 3 weeks after each dose. The severity and incidence of unsolicited AEs in the Vaxzevria group were generally lower after the second dose than after the first dose. In the Vaxzevria group, the severity and incidence of unsolicited AEs were lower in the Subcohort D2, which included participants ≥70 years old, than in Cohort C or Subcohort D1.

The major solicited local AEs (≥20%) after the first or second dose of Vaxzevria in Japanese Study D8111C00002 were injection site pain and tenderness, and the major solicited systemic AEs (≥20%) were malaise, myalgia, fatigue, and headache (see Table 17 in Section 7.1.1). These results were similar to those of the pooled analysis. As for the timing of onset, both in the results of Japanese participants and the pooled analysis, the incidence was highest within 2 days after vaccination and decreased by 6 to 7 days after vaccination, suggesting the short duration. The major unsolicited AEs in Japanese participants were consistent with events commonly reported after prophylactic vaccination against infections. Also, there was no clear imbalance between the Vaxzevria and placebo groups in the types or incidence of events that are generally considered unrelated to vaccination. These results were consistent with the findings in the pooled analysis. As described above, the safety profile of Vaxzevria in the Japanese was almost the same as that seen in the pooled analysis, and therefore there appears to be no safety concerns specific to the Japanese population.

7.R.3.1.2 Serious adverse events and adverse reactions

The applicant's explanation about the occurrence of serious adverse events (SAEs) and adverse reactions:
In the Any Dose for Safety Analysis Set in the pooled analysis, the incidence of serious events was 108 of 12,282 (0.9%) participants in the Vaxzevria group and 127 of 11,962 participants in the placebo group (72 of 5,744 participants [1.3%] in the meningococcal vaccine 2-dose group, 45 of 5,209 participants [0.9%] in the meningococcal vaccine + placebo group, and 10 of 1,009 participants [1.0%] in the placebo 2-dose group) (see Section 7.1.1). Of these, the events in the following participants were considered related to the study vaccine: 2 participants (pyrexia [Grade 4 (40.5°C)] in 1 participant and myelitis transverse [Grade 3] in 1 participant) in the Vaxzevria group; and 2 participants (autoimmune haemolytic anaemia [Grade 2] in 1 participant and myelitis [Grade 3] in 1 participant, both in the meningococcal vaccine 2-dose group) in the control group. The outcomes of these events were as follows: pyrexia in the Vaxzevria group, resolved on the same day; myelitis transverse, "unknown" at the time of database lock with the final outcome "not resolved"; autoimmune haemolytic anaemia in the control group, "resolved" 55 days after the study vaccination; myelitis, "unknown" at the time of database lock with the final outcome "not resolved."

Potential immune-mediated neurologic conditions reported as SAEs occurred in 3 participants (see Section 7.R.3.2 for these events).

At the time of data cutoff, SAEs leading to death were reported in 7 participants: 2 in the Vaxzevria group (respiratory tract infection fungal in a participant who was diagnosed with HIV infection after the start of study; metastatic neoplasm in 1 participant), 1 in the meningococcal vaccine 2-dose group (craniocerebral injury), 2 in the meningococcal vaccine + placebo group (COVID-19 pneumonia in 1 participant; haematological malignancy in 1 participant), and 2 in the placebo 2-dose group (injury in 1 participant; homicide in 1 participant). None of these SAEs leading to death were considered related to the study vaccination.

In Japanese Study D8111C00002, no deaths were reported up to 56 days after the first dose of study vaccine. An SAE occurred in 1 participant in the placebo group (Subcohort D1, severe cervical dysplasia after the first dose).The causal relationship with the study vaccine was ruled out.

7.R.3.1.3 Occurrence of adverse events by subgroup

[1] By age

The applicant's explanation about the safety of Vaxzevria by age:
Among participants evaluated for Dose 1 SD solicited AEs in the pooled analysis, the severity and incidence of solicited local and systemic AEs were lower in participants aged ≥65 years than in those aged 18 to 64 years. In all of the age subgroups, the severity and incidence of solicited AEs were lower after the second dose than after the first dose. In the Dose 1 SD for Safety Analysis Set, the incidence of unsolicited AEs reported during the 28 days after vaccination with Vaxzevria, irrespective of the dose number (first or second), was also lower in participants aged ≥65 years (29.7%) than in those aged 18 to 64 years (46.7%). The most of unsolicited AEs were mild or moderate. The incidence of Grade ≥3 unsolicited AEs was low in both participants aged ≥65 years (1.7%) and those aged 18 to 64 years (2.3%).

In the Any Dose for Safety Analysis Set in the pooled analysis, the incidence of SAEs was 0.8% (90 participants) in the Vaxzevria group and 1.0% (114 participants) in the control group among participants aged 18 to 64 years, and 1.4% (18 participants) in the Vaxzevria group and 1.3% (13 participants) in the control group among participants aged ≥65 years.

Therefore, the safety profile of Vaxzevria was similar between participants aged ≥65 years and those aged 18 to 64 years. In Japanese participants as well, the severity and incidence of AEs were lower in elderly participants than in other age groups (see Section 7.R.3.1.1 [2]).

[2] By country

The applicant's explanation about the safety profile by country:

In the pooled analysis, no clinically meaningful imbalance was observed in the results of solicited AEs by country (Table 42). The incidence of unsolicited AEs tended to be higher in Brazil than in UK and South Africa (Table 42).

In the 4 studies included in the pooled analysis, only some participants recorded solicited AEs in their diaries for 1 week after each vaccination. The proportion of participants who were given the diary was 36% in UK (Studies COV001 and COV002), 2% in Brazil (Study COV003), and 93% in South Africa (Study COV005). In 98% of participants in Brazil, all AEs were collected as unsolicited AEs. This probably resulted in a higher incidence of unsolicited AEs in Brazil than in other countries in both the Vaxzevria and control groups. In Brazil, unsolicited AEs reported by ≥3% of participants in either the Vaxzevria or control group were, in descending order of occurrence, vaccination site pain, headache, myalgia, pyrexia, chills, fatigue, and asthenia. These events were consistent with solicited AEs collected in South Africa and UK. The incidence of solicited AEs was lower in South Africa than in UK and Brazil. This result might be due to the reasons such as differences in the types of solicited AEs collected by the diary and their collection period (number of days). Study COV005 collected 5 types each of local and systemic events for 7 days, while Studies COV001, COV002, and COV003 collected 7 types of local events and 10 types of systemic events for 8 days. In South Africa, the incidence of unsolicited AEs was similar between the Vaxzevria and placebo groups. Because the majority of participants in South Africa were given a diary, most of the signs and symptoms of adverse reactions expected from Vaxzevria vaccination were reported as solicited AEs. Therefore, unsolicited AEs reported after ≥7 days following vaccination are considered unrelated to Vaxzevria.

Table 42 Summary of Solicited Adverse Events within 7 Days after Study Vaccination and Unsolicited Adverse Events within 28 Days after Study Vaccination by Country in the Pooled Analysis (Dose 1 SD for Safety Analysis Set[a], DCO2)

	After the first dose		After the second dose	
	Vaxzevria	Control[b]	Vaxzevria	Control[b]
United Kingdom (COV001, COV002)	**N = 4122**	**N = 3944**	**N = 4122**	**N = 3944**
Participants evaluated for solicited AEs	1645	1493	932	825
Solicited local AEs, n (%)	1343 (81.6)	871 (58.3)	535 (57.4)	375 (45.5)
Grade ≥3[c]	13 (0.8)	4 (0.3)	0	3 (0.4)
Solicited systemic AEs, n (%)	1312 (79.8)	968 (64.8)	515 (55.3)	387 (46.9)
Grade ≥3[c]	145 (8.8)	18 (1.2)	15 (1.6)	8 (1.0)
Unsolicited AEs, n (%)	923 (22.4)	559 (14.2)	403 (9.8)	436 (11.1)
Grade ≥3[c]	41 (1.0)	26 (0.7)	25 (0.6)	24 (0.6)
Brazil (COV003)	**N = 5205**	**N = 5209**	**N = 5205**	**N = 5209**
Participants evaluated for solicited AEs	100	100	82	70
Solicited local AEs, n (%)	81 (81.0)	57 (57.0)	46 (56.1)	13 (18.6)
Grade ≥3[c]	1 (1.0)	1 (1.0)	0	0
Solicited systemic AEs, n (%)	63 (63.0)	62 (62.0)	39 (47.6)	18 (25.7)
Grade ≥3[c]	8 (8.0)	1 (1.0)	0	0
Unsolicited AEs, n (%)	2857 (54.9)	1978 (38.0)	915 (17.6)	605 (11.6)
Grade ≥3[c]	115 (2.2)	81 (1.6)	37 (0.7)	25 (0.5)
Republic of South Africa (COV005)	**N = 990**	**N = 988**	**N = 990**	**N = 988**
Participants evaluated for solicited AEs	919	910	912	904
Solicited local AEs, n (%)	421 (45.8)	166 (18.2)	305 (33.4)	110 (12.2)
Grade ≥3[c]	24 (2.6)	9 (1.0)	18 (2.0)	4 (0.4)
Solicited systemic AEs, n (%)	476 (51.8)	312 (34.3)	301 (33.0)	243 (26.9)
Grade ≥3[c]	44 (4.8)	22 (2.4)	25 (2.7)	24 (2.7)
Unsolicited AEs, n (%)	180 (18.2)	164 (16.6)	170 (17.2)	160 (16.2)
Grade ≥3[c]	10 (1.0)	9 (0.9)	4 (0.4)	11 (1.1)

N = number of participants analyzed; n = number of participants with events

a) Solicited AEs were evaluated in participants evaluated for Dose 1 SD solicited AEs.

b) The control group was the meningococcal vaccine 2-dose group in Studies COV001 and COV002, the meningococcal vaccine + placebo group in Study COV003, and the placebo 2-dose group in Study COV005.

c) For the definition of Grade ≥3, see Tables 56-1 to 3 in Section 11.2.

As for the occurrence of AEs with Vaxzevria by race, the incidence of solicited AEs was similar in the White (94.8%), Asian (97.2%), and Mixed (92.3%) populations, but lower in the Black population (64.8%). The incidence of unsolicited AEs during the 28 days after the study vaccination was similar across all races (White [40.4%], Asian [41.6%], Black [40.2%], and Mixed [57.6%]). The difference observed between races is attributable to demographic and socioeconomic differences, and there appears to be no clinical difference in the safety profile between races.

The safety profiles were generally similar between the Japanese population (Japanese Study D8111C00002) and the pooled analysis (see Section 7.R.3.1.1 [2]).

The above results indicated that there is no clinically significant difference between countries in the safety profile of Vaxzevria.

[3] By dose interval

The applicant's explanation about the occurrence of AEs after the second dose of study vaccine by dose interval: When the dose interval in the pooled analysis was divided by 1 month, the incidence of solicited AEs was lower in participants with dose interval of <4 weeks and ≥4 weeks to <8 weeks than in participants with dose interval of ≥8 weeks to <12 weeks and ≥12 weeks (Table 43). The reason for the decrease in the incidence of solicited AEs with shorter interval of vaccination is unknown, but it may be due to some confounding factors such as differences in population characteristics. For example, the incidence of AEs generally tended to be lower in

elderly participants, and many of them (87.8%) received the second dose <6 weeks after the first dose. The incidence of unsolicited AEs also did not differ by dose interval.

Table 43 Summary of Adverse Events after the Second Dose of Vaxzevria by Dose Interval in the Pooled Analysis (Dose 1 SD for Safety Analysis Set or Any Dose for Safety Analysis Set, DCO2)

	Dose interval			
	<4 weeks	≥4 weeks to <8 weeks	≥8 weeks to ≤12 weeks	>12 weeks
Solicited local AEs[a)]	75/222 (33.8)	497/1253 (39.7)	237/338 (70.1)	77/109 (70.6)
Grade ≥3	4/222 (1.8)	14/1253 (1.1)	0	0
Solicited systemic AEs[a)]	57/223 (25.6)	511/1253 (40.8)	213/339 (62.8)	74/110 (67.3)
Grade ≥3	7/223 (3.1)	24/1253 (1.9)	6/339 (1.8)	3/110 (2.7)
Unsolicited AEs[b)]	44/282 (15.6)	965/5762 (16.7)	434/2425 (17.9)	251/1979 (12.7)
Grade ≥3	1/282 (0.4)	52/5762 (0.9)	15/2425 (0.6)	11/1979 (0.6)
Unsolicited AEs related to Vaxzevria[b)]	18/282 (6.4)	559/5762 (9.7)	291/2425 (12.0)	129/1979 (6.5)

n/N (%)
a) Participants evaluated for Dose 1 SD solicited AEs, b) Any Dose for Safety Analysis Set
For the definition of Grade ≥3, see Tables 56-1 to 3 in Section 11.2.

The above results indicates no safety concern for Vaxzevria associated with the difference in dose interval.

7.R.3.2 Adverse events of special interest and adverse reactions

In Japanese Study D8111C00002 and foreign Studies COV001, COV002, COV003, and COV005, adverse events of special interest (AESIs) were specified based on the Brighton Collaboration case definition (Safety Platform for Emergency vACcines [SPEAC] project, 2020: https://media.tghn.org/articles/COVID-19_AESIs_SPEAC_V1.1_5Mar2020.pdf [last accessed on April 6, 2021]), clinical experience, and scientific interest (see Table 61 in Section 11.4).

The applicant's explanation about the occurrence of AESIs and adverse reactions:
The incidence of AESIs in Any Dose for Safety Analysis Set in the pooled analysis was as low as 0.9% (115 of 12,282 participants) in the Vaxzevria group and 1.3% (155 of 11,962 participants) in the control group. AEs reported by ≥0.1% of participants in the Vaxzevria group included paraesthesia, hypoaesthesia, muscular weakness, and COVID-19 (see Sections 7.R.3.2.2 and 7.R.3.4). The incidences of these events were comparable to or lower than those in the control group. Also, there were no meaningful imbalances in the incidences of AESIs by category or by PT.

In Japanese Study D8111C00002, 1 participant in the Vaxzevria group experienced an AESI (mild paraesthesia of the left fingers, Subcohort D1, 2 days after the second dose) by 56 days after the first dose. This event was diagnosed by a neurologist as a mild cervical intervertebral disc protrusion, and a causal relationship with the study vaccine was ruled out. The investigator decided to withdraw the event from the AESI category after the data cut off, 56 days after the first dose.

Among the AESIs, immune reactions such as shock and anaphylaxis, nervous system AEs, and thrombotic, thromboembolic, and neurovascular AEs were examined in particular as below. The risk of disease enhancement is described in Section 7.R.3.4.

7.R.3.2.1 Immune reactions such as shock and anaphylaxis

The applicant's explanation about the occurrence of immune reactions such as shock and anaphylaxis after vaccination with Vaxzevria:

In the Vaxzevria group of the pooled analysis, 1 participant experienced non-serious Grade 2 anaphylactic reaction 63 days after the first dose. The participant developed rash and shortness of breath and had no hypotension or airway problems. The participant was treated with intramuscular adrenaline and chlorpheniramine, and recovered on the same day. At the onset of these events, the participant was being treated for tonsillitis with antibiotics. Although not included in the pre-specified AESIs, non-serious Grade 2 angioedema occurred 8 days after the first dose in 1 participant in the Vaxzevria group. This event occurred after the participant ingested crabs and resolved on the same day.

In the safety database of Vaxzevria (clinical practice, spontaneous and solicited reports, and literature), 85 events in 75 participants were collected as anaphylactic reaction (narrow), angioedema (narrow) (both SMQ), and hypersensitivity (PT) related to Vaxzevria after the start of foreign marketing (international birth date: December 29, 2020 [UK]) until February 5, 2021. Eleven participants had non-serious events and 64 had serious events. There were no deaths. The mean age was 46 years (range: 18 to 90 years), with 71 women and 4 men.

Anaphylactic reactions were reported in 14 of the 75 participants. Of these, 7 participants met Sampson criteria (*J Allergy Clin Immunol*. 2006;117:391-7) and 6 participants were women aged 28 to 60 years. The events occurred on the day of vaccination (5 participants) or the day after vaccination (2 participants). Another 7 participants did not meet the Sampson criteria; in these participants there was not sufficient information to satisfy the Sampson criteria, but a causal relationship with Vaxzevria vaccination was not ruled out. In the remaining 61 of the 75 participants, the events had limited information and/or other possible causes, or did not fall under the category of acute hypersensitivity reactions based on the onset time. In 48 of the 61 participants, there was not sufficient information to classify the events as anaphylaxis meeting the Sampson criteria.

Shock or circulatory collapse was reported in 3 participants (all females), all occurring within 0 to 1 day after vaccination. The outcome was "resolving" in 2 participants and "not resolved" in 1 participant. The events were serious in all participants. A causal relationship to Vaxzevria vaccination was not ruled out.

Angioedema or local swelling was reported in 33 of the 75 participants, including angioedema in 7 participants, lip swelling in 7 participants, swelling face in 6 participants, tongue swelling in 6 participants, eye swelling in 5 participants, pharyngeal swelling in 4 participants, mouth swelling in 2 participants, and periorbital swelling in 2 participants. In 27 of the 33 participants, the events occurred within 2 days after vaccination; in the remaining 6 participants, the time to onset was not available or the events occurred 4 days after vaccination. In 4 of the 7 participants with angioedema, the events occurred within 24 hours after vaccination, and these participants were women aged 21 to 73 years. The events in the 7 participants were all serious, including a life-threatening event in 1 participant.

Based on the information obtained after the start of foreign marketing (international birth date: December 29,

2020 [UK]) until February 28, 2021, 522 events related to anaphylaxis (including 18 events of shock, shock symptoms, and circulatory collapse) have been reported, including 408 serious events.

The causal relationship between serious hypersensitivity/anaphylactic reactions and Vaxzevria cannot be ruled out and these events are considered as important identified risks. Through the package insert, etc., the applicant will issue precautionary statements that Vaxzevria should not be administered to individuals with a clear history of anaphylactic reactions to any ingredients of Vaxzevria, and that preparations should be made before vaccination to provide appropriate treatment for anaphylactoid symptoms.

PMDA reviewed the occurrence of immune reactions such as shock and anaphylaxis in clinical studies and foreign post-marketing settings and accepted the applicant's explanation that these events would be listed in the package insert as important identified risks of Vaxzevria to raise awareness. Prior to vaccination with Vaxzevria, it is desirable to check the medical history of the person to be vaccinated and monitor them for a certain period of time after vaccination. It is also necessary to provide information that appropriate measures should be taken in the event of any abnormality.

7.R.3.2.2 Nervous system adverse events

The applicant's explanation about the occurrence of nervous system AEs after vaccination with Vaxzevria:
In the pooled analysis, neurological AEs and potential immune-mediated neurological conditions reported in ≥5 participants in the Vaxzevria group, by PT, were paraesthesia (0.3% [42 participants] in the Vaxzevria group and 0.4% [51 participants] in the control group, the same order hereinafter), hypoaesthesia (0.1% [15 participants], 0.2% [20 participants]), and muscular weakness (0.1% [7 participants], 0.1% [9 participants]).

Serious potential immune-mediated neurological conditions were reported in 2 participants in the Vaxzevria group (myelitis transverse and multiple sclerosis) and 1 participant in the control (meningococcal vaccine) group (myelitis). The myelitis transverse and myelitis were resolving, and the multiple sclerosis resolved. A causal relationship with the study vaccines could not be ruled out for myelitis transverse in the Vaxzevria group and myelitis in the control group. Multiple sclerosis was considered unrelated to the study vaccine.

Facial palsy was observed in 4 participants in the Vaxzevria group and 3 participants in the control group. All of the events were non-serious. In the Vaxzevria group, the event in 3 participants occurred after the first dose (approximately 3 months, approximately 80 days, and 2 days) and the event in 1 participant occurred 21 days after the second dose (51 days after the first dose). All participants were received steroid therapy, leading to the outcome of "resolved" in 1 participant and "resolving" in 3 participants.

In the Vaxzevria group, serious VIth nerve paralysis (abducent nerve paralysis) was observed approximately 3 months after the second dose. The outcome was "not resolved," and the causal relationship with Vaxzevria was ruled out.

In Japanese Study D8111C00002, mild paraesthesia of the left fingers developed in 1 participant in the

Vaxzevria group as described above. However, the participant was diagnosed as having the symptom of cervical intervertebral disc protrusion, and a causal relationship with Vaxzevria was ruled out. The investigator decided to withdraw the event from the AESI category after the data cut off, 56 days after the first dose.

Based on spontaneous reports after permission to use or market launch in foreign countries (reporting period: January 1 to February 28, 2021), 101 immune-mediated neurologic events were reported, 86 of which were serious. The breakdown by PT included neuralgia (54 events), multiple sclerosis and neuropathy peripheral (8 events each), Guillain-Barre syndrome and sensory loss (6 event each), sensory disturbance (5 events), multiple sclerosis relapse and myelitis transverse (4 event each), optic neuritis (3 events), and encephalitis, encephalopathy, and peripheral sensorimotor neuropathy (1 event each). Of these, serious events were neuralgia (48 events), neuropathy peripheral (7 events), Guillain-Barre syndrome (6 events), multiple sclerosis (5 events), multiple sclerosis relapse (4 events), myelitis transverse and sensory loss (4 events each), sensory disturbance (3 events), optic neuritis (2 events), and encephalitis, encephalopathy, and peripheral sensorimotor neuropathy (1 event each). Other nervous system disorders by PT included seizure (77 events), facial paralysis (39 events), epilepsy (15 events), facial paresis (9 events), generalized tonic-clonic seizure (5 events), tonic convulsion (3 events), narcolepsy (2 events), febrile convulsion (2 events), status epilepticus (2 events), and clonic convulsion (1 event). All of these events were serious, except for facial paralysis (6 events), facial paresis (2 events), and epilepsy (1 event).

For most neurologic events, the number of events observed was smaller than expected from the background incidence rates based on literature, etc., and the relationship between neurological symptoms and Vaxzevria has not been established. However, because serious demyelinating events have been reported after Vaxzevria vaccination in the pooled analysis, precautionary statements will be included in the package insert, etc. In addition, immune-mediated neurologic reactions will be selected as an important potential risks in the risk management plan (RMP).

PMDA accepted the applicant’s explanation about nervous system AEs. However, nervous system AEs such as serious demyelinating events have occurred after vaccination with Vaxzevria in clinical studies and foreign post-marketing settings; this information should be disseminated through the package insert or other materials.

7.R.3.2.3 Thrombotic, thromboembolic, and neurovascular events

The applicant’s explanation about the occurrence of thrombotic, thromboembolic, and neurovascular events after vaccination with Vaxzevria:

In the pooled analysis, the thrombotic, thromboembolic, and neurovascular events reported in ≥1 participant in the Vaxzevria group, by PT, were coronary artery occlusion (1 participant in the Vaxzevria group and 1 participant in the control group, the same order hereinafter), ischaemic stroke (1 participant, 0 participants), pulmonary embolism (1 participant, 1 participant), thrombosis (1 participant, 0 participants), blindness transient (1 participant, 1 participant), myocardial infarction (1 participant, 1 participant), and transient ischaemic attack (1 participant, 4 participants). All of these events were considered unrelated to Vaxzevria.

No corresponding events occurred in Japanese Study D8111C00002.

According to spontaneous reports after permission to use or market launch in foreign countries, 294 embolic or thrombotic events (SMQ) were collected from 267 individuals by March 8, 2021 in the foreign post-marketing setting. Of these, 287 events were serious and 7 were non-serious. In addition, pulmonary embolism was reported in 2 individuals between March 9 and 10, 2021. These 296 events in 269 participants are summarized in Table 44.

Table 44 Embolic or Thrombotic Events Reported by March 10, 2021 in the Foreign Post-marketing Setting

Event term (PT, MedDRA/J ver. 23.1)	Number of events	Number of individuals with serious events
Total number of events	296	281
Acute myocardial infarction	5	5
Amaurosis fugax	2	2
Aortic embolus	1	1
Blindness transient	3	3
Brain stem infarction	1	1
Brain stem stroke	1	1
Cerebral infarction	1	1
Cerebral thrombosis	2	2
Cerebral venous sinus thrombosis	4	4
Cerebrovascular accident	59	53
Cerebrovascular disorder	1	1
Deep vein thrombosis	18	15
Diplegia	9	8
Disseminated intravascular coagulation	1	1
Embolic stroke	1	1
Embolism	1	1
Embolism arterial	1	1
Haemorrhagic infarction	1	1
Haemorrhagic stroke	3	3
Hemiparesis	15	15
Hemiplegia	6	6
Hepatic vein thrombosis	1	1
Ischaemic stroke	11	11
Mesenteric vein thrombosis	1	1
Monoparesis	10	10
Monoplegia	33	31
Myocardial infarction	34	34
Paraparesis	2	2
Paraplegia	1	1
Paresis	3	2
Pelvic venous thrombosis	1	1
Portal vein thrombosis	1	1
Pulmonary embolism	22	22
Pulmonary infarction	1	1
Quadriplegia	1	1
Splenic infarction	1	1
Splenic vein thrombosis	1	1
Superior sagittal sinus thrombosis	1	1
Thrombophlebitis	1	1
Thrombophlebitis superficial	2	0
Thrombosis	3	3
Transient ischaemic attack	28	28
Vascular stent occlusion	1	1

Of the 269 individuals, 95 were male, 166 were female, and the sex was unknown in 8. The outcome was “not resolved” in 75 individuals, “resolved” in 44 individuals, “resolving” in 73 individuals, “resolved with sequelae” in 13 individuals, “unknown” in 24 individuals, and “death” in 39 individuals. Of the individuals with fatal outcome, 18 died of myocardial infarction, 10 were aged ≥70 years, and 5 had a history of heart disease, aortic stenosis, hypertension, diabetes mellitus, and hyperlipidaemia. In 8 individuals, the cause of death was cerebrovascular disorder, and all of them were aged ≥79 years. The other causes of death included pulmonary embolism/infarction in 6 individuals, cerebral thrombosis in 2 individuals, transient ischaemic attack/lymphoproliferative disorder (remission)/asthenia in 1 individual, cardiac arrest in 1 individual, brain stem infarction/superior sagittal sinus thrombosis/haemorrhage intracranial/cerebral haemorrhage in 1 individual, death/aortic embolus in 1 individual, haemorrhagic stroke in 1 individual, and death in 1 individual. Of these, the numbers of stroke and other cerebrovascular events (73 events) and venous thromboembolism (13 events of deep vein thrombosis and 16 events of pulmonary embolism) were both lower than those predicted

from the background incidence rates based on the literature, etc., and no pattern or risk factors were observed for thrombotic events.

Further investigation was conducted on deep vein thrombosis (DVT), pulmonary embolism (PE), and cerebral venous sinus thrombosis (CVST) reported in the foreign post-marketing setting. Between January 1 and March 24, 2021, DVT, PE, and CVST were reported in 241, 292, and 72 individuals, respectively. The applicable CVST cases were searched and expanded to include cerebral venous thrombosis (CVT). The cases of PT "cerebral thrombosis" include 5 cases receiving medical review.

DVT occurred in 117 male individuals (48.5%), 122 female individuals (50.6%), and 2 individuals of unknown sex (0.8%). The age distribution: 11 individuals (4.6%) in their 20s, 18 individuals (7.5%) in their 30s, 27 individuals (11.2%) in their 40s, 33 individuals (13.7%) in their 50s, 61 individuals (25.3%) in their 60s, 55 individuals (22.8%) in their 70s, 13 individuals (5.4%) in their 80s, 8 individuals (3.3%) in their 90s, and 15 individuals (6.2%) with unknown age. The number of days from vaccination with Vaxzevria to the onset was ≤14 days post-vaccination for 136 events, ≥15 days and ≤28 days for 34 events, ≥29 days for 17 events, and unknown for 97 events (including overlapped cases). The outcome was "resolved" for 15 events, "resolving" for 131 events, "not resolved" for 75 events, "with sequelae" for 6 events, "death" for 2 events, and "unknown" for 55 events (including overlapped cases). Table 45 shows individuals with an outcome of death.

PE occurred in 128 males (43.8%), 157 females (53.8%), and 7 individuals of unknown sex (2.4%). The age distribution: 1 individual (0.3%) in their 10s, 12 individuals (4.1%) in their 20s, 21 individuals (7.2%) in their 30s, 30 individuals (10.3%) in their 40s, 40 individuals (13.7%) in their 50s, 62 individuals (21.2%) in their 60s, 66 individuals (22.6%) in their 70s, 27 individuals (9.2%) in their 80s, 5 individuals (1.7%) in their 90s, and 28 individuals with unknown age (9.6%). The number of days from vaccination with Vaxzevria to the onset was ≤14 days post-vaccination for 137 events, ≥15 days and ≤28 days for 46 events, ≥29 days for 32 events, and unknown for 81 events (including overlapped cases). The outcome was "resolved" for 17 events, "resolving" for 121 events, "not resolved" for 50 events, "with sequelae" for 21 events, "death" for 33 events, and "unknown" for 52 events (including overlapped cases). Table 46 shows individuals with an outcome of death.

CVST occurred in 15 males (20.8%), 54 females (75.0%), and 3 individuals of unknown sex (4.2%). The age distribution: 1 individual (1.4%) in their 10s, 12 individuals (16.7%) in their 20s, 16 individuals (22.2%) in their 30s, 14 individuals (19.4%) in their 40s, 12 individuals (16.7%) in their 50s, 4 individuals (5.6%) in their 60s, 0 individuals (0.0%) in their 70s, 2 individuals (2.8%) in their 80s, 0 individuals (0.0%) in their 90s, and 11 individuals (15.3%) with unknown age. The number of days from vaccination with Vaxzevria to the onset was ≤14 days post-vaccination for 40 events, ≥15 days and ≤28 days for 3 events, ≥29 days for 5 events, and unknown for 31 events (including overlapped cases). The outcome was "resolved" for 2 events, "resolving" for 8 events, "not resolved" for 34 events, "death" for 14 events, and "unknown" for 20 events (including overlapped cases). Table 47 shows individuals with an outcome of death.

Table 45 Listing of DVT Deaths

Age	Sex	TTO	Medical history	Other AEs	Country reported
60s	Female	10	Epilepsy	None	UK
80s	Female	25	Unknown	Pulmonary embolism	UK

TTO (time to onset): number of days from vaccination with Vaxzevria to onset

Table 46 Listing of PE Deaths

Age	Sex	TTO	Medical history	Other AEs	Country reported
80s	Female	3	COVID-19 immunity	Death, cardiac failure acute, multiple organ dysfunction syndrome, mitral valve incompetence, pneumothorax	UK
70s	Female	4	Type 2 diabetes mellitus, cerebrovascular accident, essential hypertension, hypothyroidism	Pain in extremity, deep vein thrombosis, hypotension, peripheral swelling, dyspnoea, hypoxia	UK
80s	Female	Unknown	Myocardial infarction, macular degeneration, cholecystectomy, transient ischaemic attack, myocardial ischaemia, gastrooesophageal reflux disease	COVID-19, gastroenteritis viral, cough, pyrexia	UK
40s	Female	Unknown	Unknown	Disseminated intravascular coagulation	Austria
70s	Female	4	Unknown	Malaise	UK
70s	Female	2	Pulmonary embolism	Malaise, lethargy	UK
60s	Female	Unknown	Gingival bleeding, epistaxis, cervical conisation	Thrombocytopenia, cerebral venous sinus thrombosis, acute myocardial infarction, vomiting, cerebral haemorrhage, retroperitoneal haemorrhage, transverse sinus thrombosis, pyrexia, headache, diarrhoea, abdominal pain, dizziness, influenza-like illness, nausea, diplopia, cold sweat	Sweden
80s	Male	28	Thrombosis, diabetes mellitus, chronic obstructive pulmonary disease, lower respiratory tract infection, dyspnoea	Headache	UK
60s	Male	6	Cellulitis	Pulse absent, deep vein thrombosis, seizure	UK
70s	Male	Unknown	Atrial fibrillation, ischaemic stroke, hemiplegia, amnesia, Dementia Alzheimer's type	None	UK
80s	Female	9	Rheumatoid arthritis	Cardiac arrest	UK
90s	Female	3	Dementia, traumatic lung injury, immobile, hip fracture, tuberculosis, pulmonary tuberculosis, peptic ulcer, internal fixation of fracture, cachexia, drug hypersensitivity, non-tobacco user, hysterosalpingo-oophorectomy, food allergy	Sudden death, tachycardia, dyspnoea, condition aggravated	Croatia
50s	Male	15	Type 2 diabetes mellitus, inflammation, chronic sinusitis, neuralgia	Deep vein thrombosis, cardiac arrest	UK
70s	Female	12	Myocardial ischaemia, fall, chronic obstructive pulmonary disease, hypothyroidism, hyperlipidaemia	Joint swelling, fall	UK
80s	Female	Unknown	Unknown	Deep vein thrombosis	UK
70s	Male	22	Unknown	None	UK
Unknown	Male	Unknown	Hypertension	Thrombosis	UK
30s	Female	Unknown	Unknown	None	Germany
50s	Female	11	Unknown	Haemorrhagic stroke, aphasia, acute coronary syndrome, disseminated intravascular coagulation, coma, hemiplegia	Italy
70s	Male	10	Unknown	Angina pectoris	UK
80s	Male	23	Pulmonary embolism	Headache, fatigue, pyrexia, chills, malaise, fatigue	UK
Unknown	Male	Unknown	Unknown	Discomfort	UK
60s	Female	14	Pulmonary embolism	None	UK
70s	Male	2	Pulmonary embolism, chronic kidney disease	Dyspnoea	UK
10s	Female	Unknown	Obesity	None	UK
60s	Male	3	Cardiomegaly, myocardial ischaemia	Myocardial ischaemia	UK
70s	Male	24	Hypertension, dementia, type 2 diabetes mellitus	None	UK
80s	Female	2	Unknown	Circulatory collapse, chest discomfort, dyspnoea, feeling hot, death, malaise	UK
90s	Female	Unknown	Dementia, asthenia, pulmonary embolism	None	UK
70s	Male	23	Suspected COVID-19	COVID-19, nausea	UK

Age	Sex	TTO	Medical history	Other AEs	Country reported
60s	Female	Unknown	Aortic aneurysm, hypertension, knee arthroplasty	Sudden death	UK
70s	Female	15	Unknown	None	Latvia
80s	Female	15	Rheumatoid arthritis, pulmonary atypical adenomatous hyperplasia, osteoarthritis, emphysema, osteoporosis postmenopausal, cardiac valve prosthesis user, goitre, plasma cell myeloma, essential hypertension, device failure, spinal osteoarthritis, type 2 diabetes mellitus, spinal compression fracture, anaemia, cardiac failure chronic	Dyspnoea	Latvia

TTO (time to onset): number of days from vaccination with Vaxzevria to onset

Table 47 Listing of CVST Deaths

Age	Sex	TTO	Medical history	Other AEs	Country reported
40s	Female	9	Asthma, autoimmune thyroiditis, intervertebral disc protrusion	Acute respiratory failure, gait disturbance, vomiting, pain in extremity, thrombocytopenia, coordination abnormal, seizure, chills, headache, dizziness, hemiparesis, pyrexia	Germany
60s	Female	Unknown	Gingival bleeding, epistaxis, cervical conisation	Thrombocytopenia, pulmonary embolism, acute myocardial infarction, vomiting, cerebral haemorrhage, retroperitoneal haemorrhage, pyrexia, headache, diarrhoea, abdominal pain, dizziness, influenza-like illness, nausea, diplopia, cold sweat	Sweden
Unknown	Female	Unknown	Unknown	Thrombocytopenia, disseminated intravascular coagulation, venous thrombosis, arterial thrombosis, coagulopathy	Denmark
30s	Female	7	Unknown	Brain death, haemorrhage intracranial, thrombocytopenia	Germany
20s	Male	Unknown	Immune thrombocytopenia, steroid therapy, cholangitis sclerosing, autoimmune hepatitis, migraine	Immune thrombocytopenia, subdural haematoma, seizure, headache, brain death	UK
60s	Female	13	Hiatus hernia, suppressed lactation, osteoarthritis, gastric ulcer, glucose tolerance impaired	Cerebral infarction, thrombocytopenia, depressed level of consciousness, thrombosis, headache	UK
40s	Female	11	Unknown	Haemorrhagic cerebral infarction, thrombocytopenia, cerebral haematoma	Norway
30s	Female	7	Hypersensitivity	Brain oedema, subarachnoid haemorrhage, cerebellar haematoma, disseminated intravascular coagulation, thrombocytopenia	Norway
50s	Female	10	Unknown	Cerebral infarction, cerebral haemorrhage	Italy
40s	Female	10	Unknown	Respiratory failure, thrombocytopenia, haemorrhagic transformation stroke, thrombotic stroke, brain oedema, gastric haemorrhage, depressed level of consciousness, hypercoagulation, pulmonary congestion, petechiae, headache, brain compression, cerebral circulatory failure	Poland
40s	Female	11	Hypertension, Crohn's disease, inflammatory bowel disease, pre-eclampsia, hypertension	Coagulopathy, aphasia, platelet count decreased, cerebral haemorrhage, visual brightness, hallucination, hemiplegia, loss of consciousness, visual impairment, photophobia, hyperacusis, thrombosis, headache, dizziness	UK
Unknown	Male	Unknown	Brain death	Thrombotic thrombocytopenic purpura, headache, cerebral haemorrhage	UK
Unknown	Female	Unknown	Thrombotic thrombocytopenic purpura, headache, cerebral haemorrhage	Venous haemorrhage	UK
60s	Female	9	Unknown	Thrombocytopenia, muscular weakness, haematoma, vomiting, dizziness, somnolence	UK

TTO (time to onset): number of days from vaccination with Vaxzevria to onset

The background incidences of DVT, PE, and CVST in Japan and overseas were searched, and the results are shown below.

In US, the annual incidence rate of DVT is estimated to be 80 per 100,000 persons (*Chest*. 2012;141 Suppl:e419S-e496S). In US, venous thrombosis occurs in >200,000 people every year, including 50,000 people complicated with pulmonary embolism. The incidence rate increases over time with aging (*Chest*. 2016;149:315-52). In Japan, 14,674 people are estimated to experience DVT annually, with an annual incidence

rate of 12 per 100,000 persons, according to the short-term questionnaire survey conducted in a research on blood coagulation abnormalities by the Ministry of Health, Labour and Welfare in 2006, (Guidelines for Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis [JCS 2017]).

Between 1997 and 2015, 464,046 people (53.9% women) in UK were diagnosed with PE and hospitalized (*Chest*. 2012;141 Suppl:e419S-e496S). The annual number of hospitalizations due to PE became more than double during this period, and the incidence rate of PE increased from 50.2 to 97.8 per 100,000 person-years. The incidence rate of PE increased in all age groups and was highest in the elderly. In Japan, 7,864 people experienced PE in 2006 (*Circ J*. 2009;73:305-9), which is estimated to be 62 per 1 million population. Compared with the incidence in US, approximately 500 per 1 million population, the incidence per population in 2006 was approximately 1/8 of that in US (Guidelines for Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis [JCS 2017]). In Japanese people, acute PTE is more common in women than in men, with its peak in 60s to 70s (*Clin Cardiol*. 2001;24:132-8).

There are no reports on incidence rates specific to CVST. However, in a retrospective study involving all patients hospitalized at an early acute hospital in Norway between 2011 and 2017, the incidence rate [95% CI] of CVT by age and by sex was 1.39 [0.73, 2.42] per 100,000 person-years in men and 2.22 [1.34-3.48] per 100,000 person-years in women at 18 to 49 years old and 2.35 [1.31 -3.92] per 100,000 person-years in men and 1.86 [0.98-3.24] per 100,000 person-years in women at ≥50 years old (*Stroke*. 2020;51:3023-9). In Japan, no reports on the incidence rate of CVST were found.

The above results indicated that it is unnecessary to newly provide precautions at this point, but these events will be further monitored and evaluated as a type of AESIs.

PMDA confirmed the following trends in European authorities, etc. related to thrombotic, thromboembolic, and neurovascular events reported in foreign post-marketing settings (as of the end of March 2021):

On March 7, 2021, the Austrian regulatory authority announced that vaccination with Vaxzevria was suspended in response to the development of thrombotic events in 2 individuals after administration of Vaxzevria (https://www.basg.gv.at/en/market-surveillance/official-announcements/detail/zwischenfaelle-nach-impfung-mit-covid-19-impfstoff-von-astrazeneca [last accessed on April 6, 2021]). Subsequently, because similar cases were reported in other European countries, vaccination with Vaxzevria was suspended in pertinent countries.

According to EMA report,[28)] approximately 20 million people had received Vaxzevria in UK and EU/EEA as of March 14, 2021. Approximately 9.7 million doses had been administered in UK as of February 28, 2021, and >5.5 million doses in the EU/EEA as of March 11, 2021. As of March 16, 2021, 469 thromboembolic events (including 276 from UK) were noted following vaccination with Vaxzevria by retrieval in EudraVigilance. Of these, 436 (93%) events were serious and 59 (13%) cases had an outcome of death. The majority of these cases (63%) were female with a mean age of 60 years. The number of these events was smaller than that estimated in

28) EMA, Signal assessment report on embolic and thrombotic events (SMQ) with COVID-19 Vaccine (ChAdOx1-S [recombinant]) – COVID-19 Vaccine AstraZeneca (Other viral vaccines) (https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant-covid_en.pdf [Last accessed on April 6, 2021])

the general population, and there was no sufficient evidence to suggest a relationship between Vaxzevria and an increased risk of thromboembolic events. However, signals for very rare events also have been detected in these events, and 7 events of disseminated intravascular coagulation (DIC) and 18 events of CVST (including CVT and cerebral thrombosis) were reported. Of these events, 4 events of DIC and 6 events of CVST resulted in death. Most of the events occurred in women aged ≤55 years, which may reflect an imbalance in the population that received Vaxzevria. The majority occurred within 14 days of vaccination with Vaxzevria. These events are very rare and difficult to compare with the spontaneous incidence in individuals who were not vaccinated. However, based on the data before the COVID-19 epidemic, the number of DIC cases estimated to be reported in UK and EEA by March 16 from individuals aged <50 years who received Vaxzevria within 14 days was approximately 2 cases (actually 5 cases), and the number of CVST cases estimated in the same way was approximately 3.3 cases (actually 13 cases). For CVST, additional 8 cases were reported from EU/EEA countries after data lock of the investigation with EudraVigilance, and no sufficient information has been available for these cases.

In light of the above discussions, EMA announced on March 18, 2021 that preliminary assessment did not suggest that Vaxzevria increases the risks of overall thrombotic events and that the benefits of Vaxzevria administration still outweigh the risks of AEs (https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots [last accessed on April 6, 2021]). On the other hand, EMA considered that the association between Vaxzevria and very rare thrombotic events accompanied by thrombocytopenia, including CVST, could not be ruled out and that further evaluation would be required. Precautions have been provided to healthcare professionals to instruct vaccine recipients to immediately see a doctor if they experience shortness of breath, chest pain, swelling of legs, persistent abdominal pain, severe or persistent headache, or vision blurred after vaccination with Vaxzevria, or if they experience contusion (petechiae) beyond the injection site several days after vaccination with Vaxzevria.

As of April 7, 2021, most EU countries have resumed vaccination with Vaxzevria. However, some countries have set age limits for Vaxzevria, and some have announced continued suspension.

PMDA's view:
The causal relationship between Vaxzevria and thrombotic, thromboembolic, and neurovascular events is unknown at this point. However, multiple thrombotic, thromboembolic, and neurovascular events occurred after vaccination with Vaxzevria in clinical studies and after the market launch in foreign countries. Further, the seriousness of these events should be taken into account. Therefore, it is necessary to investigate their occurrence after the market launch while setting these events as a post-marketing safety specification for Vaxzevria. These events that have been reported in the foreign post-marketing setting include rare events such as CVST. Many of such events have occurred in non-elderly individuals. Therefore, the package insert and other materials should provide the following information: the fact that thrombotic, thromboembolic, and neurovascular events have been reported after vaccination with Vaxzevria; the details of the events; the age groups that experienced the events; timing of onset (mostly within 14 days after administration of Vaxzevria); and initial symptoms.

The above conclusion of PMDA will be finalized, taking account of comments raised in the Expert Discussion.

7.R.3.3 Safety in special populations

Safety in individuals with underlying disease, elderly people, and pregnant women was investigated as below.

7.R.3.3.1 Safety in individuals with underlying diseases

PMDA asked the applicant to explain the safety of Vaxzevria in vaccine recipients with underlying diseases at high risk of severe COVID-19 who are in great need of SARS-CoV-2 vaccines.

The applicant's explanation:

For the 4 clinical studies used in the pooled analysis, information on the participants who had pre-specified underlying diseases and characteristics at baseline was collected as risk factors for severe COVID-19, occurrence of complications, and death. These underlying diseases include cardiovascular disease (including hypertension and other cardiovascular diseases), respiratory disease, type 2 diabetes mellitus, and BMI ≥30 kg/m^2. More than one-third of the participants (36.5% for the Vaxzevria group and 36.7% for the control group) had underlying medical conditions at baseline that were considered a risk factor for COVID-19. The details were mainly obesity (54.5%), hypertension (25.5%), and asthma (18.8%).

The incidence and severity of solicited or unsolicited AEs in participants with underlying diseases were similar to those in participants without underlying diseases at baseline. No data are available on the safety of Vaxzevria in participants with malignant tumors, chronic obstructive pulmonary disease, chronic kidney disease, or immunocompromised state due to solid organ transplant as underlying medical conditions. However, there is no evidence to suggest that the safety in these participants differs from that in the general population.

Safety information is insufficient for individuals with severe or poorly-controlled underlying disease and those with severe immunodeficiency, and the safety in such individuals may differ from that in the general population. Therefore, the information of these individuals will be specified as important missing information in the RMP, and the necessity of additional safety measures will be examined by collecting information in the post-marketing clinical practice.

PMDA accepted the applicant's explanation. However, the clinical studies enrolled participants with underlying diseases in relatively stable condition, but individuals with various underlying diseases are expected to receive vaccination in the post-marketing setting. Therefore, it is necessary to continue collecting and evaluating information on the safety of Vaxzevria in vaccine recipients with underlying diseases at high risk of severe COVID-19 who are in great need of Vaxzevria.

7.R.3.3.2 Safety in the elderly

The applicant's explanation about the safety in the elderly:

In the pooled analysis and Japanese Study D8111C00002, the safety profiles of Vaxzevria were generally comparable between the elderly and young adults, with lower incidences of AEs in the elderly (see Section 7.R.3.1.3).

Of overall participants in the 4 studies used in the pooled analysis, participants aged ≥65 years accounted for 9.4% and those aged ≥70 years 6.4%, showing a small proportion of elderly participants. Also, the follow-up period was shorter in elderly participants than in other populations. Therefore, the safety information after permission to use in foreign countries was also investigated.

Based on spontaneous reports after permission to use or market launch in foreign countries (reporting period: January 1 to February 28, 2021), 14,303 AEs were spontaneously reported in elderly people after approval in foreign countries. The major adverse reactions are shown in Table 48. There is no trend different from the safety profile reported in clinical studies, considering the following: (a) many reports were from general vaccine recipients without medical confirmation; (b) the definition of seriousness can be different from that of medically confirmed reports; and (c) many of elderly people have pre-existing medical conditions.

The above results indicated that no new safety concerns have been observed in the elderly compared with the non-elderly, and at present, there are no events requiring caution for the elderly.

Table 48 Adverse Reactions (PT) with ≥50 Episodes Reported in Elderly Participants Aged ≥65 Years in the Foreign Post-marketing Setting (Period: January 1, 2021 - February 28, 2021)

SOC	PT (MedDRA/J Ver. 23.1)	Number of adverse reactions	Number of elderly individuals with serious adverse reactions
Cardiac disorders	Palpitations	73	61
Gastrointestinal disorders	Abdominal pain	82	70
	Abdominal pain upper	77	63
	Diarrhoea	256	204
	Nausea	785	714
	Vomiting	378	322
General disorders and administration site conditions	Asthenia	126	115
	Chest pain	52	45
	Chills	1067	935
	Death	132	131
	Fatigue	965	838
	Feeling cold	167	147
	Illness	103	97
	Influenza like illness	232	197
	Malaise	404	348
	Pain	169	144
	Pyrexia	1200	1014
Infections and infestations	Influenza	190	167
Injury, poisoning and procedural complications	Injection related reaction	55	47
Metabolism and nutrition disorders	Decreased appetite	161	149
Musculoskeletal and connective tissue disorders	Arthralgia	413	372
	Back pain	74	64
	Myalgia	423	379
	Pain in extremity	236	180
Nervous system disorders	Dizziness	341	298
	Headache	1691	1465
	Lethargy	112	95
	Paraesthesia	62	53
	Syncope	71	62
	Tremor	403	361
Psychiatric disorders	Confusional state	79	67
Respiratory, thoracic and mediastinal disorders	Cough	54	46
	Dyspnoea	100	80
	Oropharyngeal pain	51	41
Skin and subcutaneous tissue disorders	Hyperhidrosis	153	134
	Pruritus	66	47
	Rash	82	40

The safety results in clinical studies indicate that the severity and incidence of solicited local and systemic AEs and the incidence of unsolicited AEs were lower in the elderly aged ≥65 years than in individuals aged 18 to 64 years, and the reported AEs were similar between the 2 age groups. Therefore, PMDA concluded that no further caution is required in the elderly aged ≥65 years compared with individuals aged 18 to 64 years.

7.R.3.3.3 Safety in pregnant women

The applicant's explanation about the safety in pregnant women:

In the 4 foreign studies included in the pooled analysis, women who were pregnant, lactating, or wishing to become pregnant were excluded. Also, women of childbearing potential were required to continuously use highly effective contraceptive methods. At the primary analysis for the pooled analysis (DCO2), 40 pregnancies were identified (24 in the Vaxzevria group and 16 in the control group). Abortion occurred in 4 participants in the Vaxzevria group and 3 participants in the control group, and spontaneous abortion occurred in 4 participants in the Vaxzevria group and 3 participants in the control group. Available data are limited for vaccination with Vaxzevria in pregnant or lactating women and women who become pregnant after vaccination with Vaxzevria.

All pregnancies will be followed up until their outcomes are confirmed. No particular concerns were noted in the reproductive and developmental toxicity study of Vaxzevria (see Section 5.5).

In spontaneous reports after permission to use or market launch in foreign countries (reporting period: January 1 to February 28, 2021), 152 AEs were reported, and there was no particular concern. Table 49 shows AEs with ≥2 episodes reported in pregnant women. No AEs have been reported in lactating women.

Table 49 Adverse Events with ≥2 Episodes Reported in Pregnant Women after Market Launch in Foreign Countries (Period: January 1, 2021 - February 28, 2021)

SOC	PT (MedDRA/J Ver. 23.1)	Number of AEs	Number of pregnant women with SAEs
Gastrointestinal disorders	Nausea	13	10
General disorders and administration site conditions	Adverse drug reaction	2	0
	Chills	10	7
	Fatigue	7	5
	Malaise	4	4
	Pain	2	1
	Pyrexia	17	10
Injury, poisoning and procedural complications	Maternal exposure during pregnancy	13	10
Musculoskeletal and connective tissue disorders	Arthralgia	4	3
	Myalgia	9	6
Nervous system disorders	Headache	14	11
	Paraesthesia	2	2
	Tremor	3	3
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	2	2
	Pregnancy	2	1
Respiratory, thoracic and mediastinal disorders	Cough	2	2
Skin and subcutaneous tissue disorders	Hyperhidrosis	4	3
	Night sweats	2	2
	Rash	3	2

In Japan, no study or post-marketing surveillance in pregnant or lactating women is planned, but Vaxzevria in such women is planned to be evaluated in post-marketing clinical studies in Europe. In addition, if AE reports are obtained from pregnant or lactating women after the market launch, a follow-up investigation including the outcome of childbirth will be conducted as a routine pharmacovigilance activity.

PMDA's view:

Pregnant or lactating women were excluded from the clinical studies submitted in this application, and there has been little use experience to date with the safety information limited. Therefore, it is necessary to specify pregnancy and lactation as important missing information and collect further information in the post-marketing setting. If new findings are obtained from the pregnancy outcome in pregnant women who received Vaxzevria in clinical studies or from the information after the market launch, it is necessary to take appropriate actions such as consideration of the necessity of additional precautions.

7.R.3.4 Risk of disease enhancement

The applicant's explanation about the risk of disease enhancement after vaccination with Vaxzevria:

Vaxzevria is considered to have a very low risk of vaccine-associated enhanced diseases (VAED), as comprehensively suggested by Th1-dominant CD4 response, production of IgG1/IgG3 antibodies, and induction

of neutralizing antibodies after the first and second doses of Vaxzevria (see Section 7.R.2.2.1.2 [2]).

The clinical studies of Vaxzevria classified VAED, including vaccine-associated enhanced respiratory disease (VAERD), as AESIs (see Table 61 in Section 11.4), and relevant information was collected. VAERD/VAED were defined as clinical symptoms with various severity and pathological changes of diseases, characterized by respiratory disease with long-term persistent pyrexia, expanding pulmonary infiltrative shadows, bronchial interstitial pneumonia, necrotising bronchiolitis, etc. (*J Gen Virol*. 2016;97:1489-99). In collecting the information on VAED, investigators were instructed to collect episodes of COVID-19, particularly ICU admission information, laboratory values including oxygen saturation, respiratory rate, and vital signs, need for oxygen therapy, need for mechanical ventilation, imaging, and blood test results.

At the primary analysis (DCO2), the number of participants with COVID-19-related AEs (PT such as COVID-19, COVID-19 pneumonia, suspected COVID-19) was smaller in the Vaxzevria group (15 participants [0.1%]) than in the control group (36 participants [0.3%]) in Any Dose for Safety Analysis Set of the pooled analysis. COVID-19 SAEs occurred in 2 participants in the Vaxzevria group and 21 participants in the control group (COVID-19 in 17 participants and COVID-19 pneumonia in 4 participants).

VAED including VAERD has been monitored as an AESI (see Table 61 in Section 11.4) since permission to use or market launch in foreign countries. Based on spontaneous reports after permission to use or market launch in foreign countries (reporting period: January 1 to February 28, 2021), there have been 43 spontaneous reports of VAED including VAERD in 43 individuals, including 28 reports in elderly individuals and 39 serious cases. The breakdown was 31 events of pneumonia, 3 events of pneumonitis, 2 events of COVID-19 pneumonia, 2 events of coagulopathy, 2 events of multiple organ dysfunction syndrome, 1 event of cardiogenic shock, 1 event of respiratory failure, and 1 event of pulmonary haemorrhage. The outcome was death in 18 of the 43 participants. Eight of the 43 participants tested positive for COVID-19 (2-26 days after the first dose) and 4 participants died; the cause of death was reported as COVID-19 pneumonia/pneumonitis. Information was limited for the timing of COVID-19 tests related to vaccination and for tests required to evaluate VAED/VAERD. However, as a result of evaluation, these reported cases did not appear to suggest a sign of VAED or VAERD.

At present, no relationship has been suggested between Vaxzevria and VAED/VAERD, and therefore providing precautions is considered unnecessary. However, since there is a theoretical concern that VAED including VAERD may develop after vaccination with Vaxzevria, VAED/VAERD are to be classified as an important potential risk in the RMP.

PMDA accepted the applicant’s explanation. However, information on the risk of disease enhancement due to Vaxzevria should be further collected in and outside Japan after the market launch and new findings should be provided promptly.

7.R.3.5 Safety information after permission to use or market launch in foreign countries

The applicant’s explanation about the safety information after permission to use or market launch in foreign countries:
As of March 27, 2021, Vaxzevria has received conditional marketing authorization or approval for emergency supply in 78 countries and WHO. In total, 116,952,960 doses are estimated to have been shipped by February 28, 2021. The percentage of the main shipment destinations (country or region) to the total shipment amount was 10.8% in UK, 9.5% in the EU, 0.4% in North America*, and 79.3% in other countries (South Korea, Australia, Thailand, Vietnam, India,* etc.) (* indicates the vaccine product of Serum Institute of India, a license partner of the applicant).

In spontaneous reports after permission to use or market launch in foreign countries (reporting period: January 1 to February 28, 2021), 53,023 AEs were collected as spontaneous reports (42,320 known events, 10,703 unknown events), including 374 deaths and 41,121 SAEs (32,652 known events, 8,469 unknown events). Of these, AESIs are presented in Section 7.R.3.2. AEs in the elderly, pregnant women, and children were presented in Sections 7.R.3.3.2, 7.R.3.3.3, and 7.R.4.2.5, respectively. The novelty of events was determined based on the latest Company Core Data Sheet (CCDS) (revised on [redacted], 20[redacted]).

Table 50 shows deaths reported in ≥5 events. Of the deaths, 125 of 236 occurred in elderly individuals aged ≥80 years. The following significant comorbidities or conditions were reported as the background of the deaths: dementia, frailty, chronic obstructive pulmonary disease, advanced malignant tumors, cerebrovascular disorder, diabetes mellitus, ischaemic heart disease, cardiac failure, atrial fibrillation, epilepsy, chronic kidney disease, and hypertension. Most of these vaccine recipients were elderly people or individuals who had a comorbidity in UK. At present, there is no particular pattern or accumulation of specific events that may pose a concern about deaths based on the post-marketing safety information.

The benefit-risk profile of Vaxzevria is considered to be still favorable based on the information obtained after permission to use or market launch in foreign countries.

Table 50 Details of Deaths Reported in ≥5 Events after Market Launch in Foreign Countries (Period: January 1, 2021 - February 28, 2021)

SOC	PT (MedDRA/J Ver. 23.1)	Number of events
Cardiac disorders	Cardiac arrest	17
	Myocardial infarction	13
Gastrointestinal disorders	Vomiting	5
General disorders and administration site conditions	Asthenia	5
	Death	150
	Malaise	8
	Pyrexia	6
	Sudden death	7
Infections and infestations	COVID-19	13
	Pneumonia	10
Nervous system disorders	Cerebrovascular accident	7
Respiratory, thoracic and mediastinal disorders	Dyspnoea	8
	Pneumonia aspiration	5

PMDA reviewed the safety information after permission to use or market launch in foreign countries. AESIs are as described in Section 7.R.3.2. AEs in the elderly, pregnant women, and children are as described in Sections 7.R.3.3.2, 7.R.3.3.3, and 7.R.4.2.5, respectively.

7.R.4 Clinical positioning and vaccination in special populations

7.R.4.1 Clinical positioning

PMDA's view on the clinical positioning of Vaxzevria is as follows:

As of April 6, 2021, 485,085 individuals have been infected with SARS-CoV-2 in Japan, with a death toll of 9,246 (https://www.mhlw.go.jp/stf/newpage_17903.html [last accessed on April 6, 2021]). The number of infected individuals is estimated to increase when including those with asymptomatic infection. The number of infections by age group was largest in people in their 20s, followed by those in their 30s, 40s, and 50s, but the numbers of deaths and severe cases were high in people in their ≥60s.
(https://www.mhlw.go.jp/content/10906000/000716059.pdf [last accessed on April 6, 2021]).

The incubation period from the exposure to SARS-CoV-2 to the onset of COVID-19 is 1 to 14 days, usually approximately 5 days (https://www.who.int/publications/i/item/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations [last accessed on April 6, 2021]). Patients with COVID-19 become infectious before symptom onset and especially highly infectious early after the onset. This is considered to be the cause of community transmission (The Clinical Guidance for COVID-19 [Version 4.2] [https://www.mhlw.go.jp/content/000742297.pdf (last accessed on April 6, 2021)]).

In Japan, remdesivir, an antiviral drug, was approved on May 7, 2020 for the treatment of disease caused by SARS-CoV-2 infection (COVID-19). Use of dexamethasone is also allowed within the scope of approved indications. Moreover, various therapeutic drugs are used in medical practice depending on the severity and symptom (The Clinical Guidance for COVID-19 [Version 4.2]). However, the numbers of infected individuals, severe cases, and fatal cases have increased despite these treatment. Although a causal relationship with COVID-19 has not been clarified, some reports state that part of infected individuals experience prolonged symptoms such as smell disorder, taste disorder, dyspnoea, and alopecia even after virus disappearance (*Open Forum Infect Dis.* 2020;7:0faa507.doi:10.1093/ofid/ofaa507). The number of infected individuals is continuously increasing

in Japan making the medical system tight. Also, if COVID-19 occurs in a person, it may become severe or result in death. Given these facts, prevention of COVID-19 is extremely important.

According to the "Vaccination Against COVID-19 (Cabinet Secretariat, Ministry of Health, Labour and Welfare, February 9, 2021)" (https://www.cas.go.jp/jp/seisaku/ful/bunkakai/wakuchin_sesyu.pdf [last accessed on April 6, 2021]), the objective of vaccination is to "prevent the onset of COVID-19, reduce the occurrence of deaths and severe cases as much as possible, and consequently prevent the spread of COVID-19." In Japan, Comirnaty Intramuscular Injection (Pfizer Japan Inc.) was approved on February 14, 2021 as a vaccine for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)." However prompt supplies of multiple types of vaccines are in demand due to the scale of SARS-CoV-2 infection, persistent and rapid spread of infections, the magnitude of effects of the pandemic on medical care and socioeconomy, and the issue on supply quantity associated with vaccinations on a global scale.

The results of the foreign pooled analysis demonstrated the effect of Vaxzevria in preventing COVID-19, and the Japanese Study D8111C00002 confirmed an increase in serum neutralizing antibody titer comparable to that in the pooled analysis. Hence, Vaxzevria is expected to have a similar preventive effect against COVID-19 in the Japanese population as well (see Section 7.R.2), and there was no concern about the safety and tolerability that affects the approval or rejection (see Section 7.R.3). Long-term efficacy and safety after vaccination with Vaxzevria and the suppressive effect against COVID-19 are currently unknown (see Sections 7.R.2 and 7.R.3). Also, the efficacy of Vaxzevria against variants is uncertain (see Section 3.R.2). However, vaccination with Vaxzevria is expected to be effective in preventing COVID-19 and to reduce the number of affected individuals in Japan.

Since Vaxzevria is a vaccine product that is refrigerated at 2 to 8°C, storage in a refrigerator is basically allowed as with the handling of general vaccines to prevent infections such as seasonal influenza vaccines used in Japan. No special measures are required for distribution, delivery, or storage beyond general vaccines for infection prevention. Therefore, Vaxzevria is considered to contribute to wide promotion of vaccination in the epidemic of COVID-19 because this product allows vaccination at many vaccination venues in a broad area and reduces the burden on people involved in the vaccination.

On the basis of the above, it is considered meaningful to make Vaxzevria available as a preventive vaccine against COVID-19 in medical practice in Japan.

7.R.4.2 Vaccination for special populations

In the post-marketing phase, Vaxzevria is assumed to be administered to people with various conditions or characteristics who were not included in the clinical studies. Therefore, PMDA conducted a review on vaccination in special populations as follows.

7.R.4.2.1 Individuals with underlying disease

The underlying diseases and characteristics that are prioritized for vaccination in Japan include malignant tumors,

chronic respiratory disease, chronic kidney disease, type 2 diabetes mellitus, hypertension, obesity with BMI ≥30 kg/m^2, and immunocompromised states
(https://www.cas.go.jp/jp/seisaku/ful/bunkakai/wakuchin_sesyu.pdf [last accessed on April 6, 2021]).

The applicant's explanation about the vaccination with Vaxzevria in individuals with these underlying diseases or characteristics:
Little clinical study data have been obtained for the efficacy and safety of Vaxzevria in individuals with underlying diseases or characteristics who are prioritized for vaccination in Japan. Some of the clinical studies of Vaxzevria enrolled participants with the following underlying diseases or characteristics at baseline: cardiovascular diseases (including hypertension and other cardiovascular diseases), respiratory diseases, type 2 diabetes, and BMI ≥30 kg/m^2. The efficacy in these populations was comparable to the preventive effect against SARS-CoV-2 infection observed in the overall population, and the safety profile was also similar (see Sections 7.R.2.2.1.1 and 7.R.3.3.1). However, since participants with severe disease were excluded from the clinical studies, the benefit-risk profile in a population with severe disease (e.g., participants with malignant tumors, chronic obstructive pulmonary disease, chronic kidney disease, or immunocompromised state due to solid organ transplant) has not been established.

Immunocompromised individuals, who were excluded from the clinical studies of Vaxzevria, generally have a higher incidence of vaccine-preventable diseases with a higher risk of deaths from such diseases. On the other hand, in severely immunocompromised individuals, the immune system does not respond sufficiently, presumably diminishing the effect of vaccine. It is unknown whether Vaxzevria induces the same immune response in individuals with impaired immune responses, including those who have received immunosuppressive drugs, as in individuals without abnormalities in the immune system. Also, the available data on the safety of Vaxzevria are limited. However, there is currently no evidence that the safety profile of Vaxzevria in these people differs from that in the general population.

For the safety of Vaxzevria in these people, investigation and information collection will be continued in the post-marketing phase. In Studies COV002 and COV005, immunogenicity and safety were investigated in medically stable HIV-positive participants, and the results will be submitted as soon as they become available.

PMDA's view:
For the efficacy and safety of Vaxzevria in individuals with underlying diseases, etc. who are prioritized for vaccination in Japan, only limited data are available from the results of clinical studies included in the clinical data package for the present application (see Sections 7.R.2.2.1.1 and 7.R.3.3.1). On the other hand, since these underlying diseases, etc. are considered to be risk factors for severe COVID-19 (The Clinical Guidance for COVID-19 [Version 4.2]) and the prevention of COVID-19 is important in individuals with these underlying diseases, Vaxzevria is highly needed. Vaxzevria is assumed to be administered when the benefit of administration is determined to outweigh the risks of Vaxzevria based on the situation or condition of individual patients. Therefore, if new findings about vaccination with Vaxzevria in individuals with underlying diseases, etc. are obtained from post-marketing surveillance or observational studies, and from the results of HIV-positive

participants in currently ongoing clinical studies, etc., the findings should be disseminated promptly.

7.R.4.2.2 Elderly

The applicant's explanation about the vaccination with Vaxzevria in the elderly:
As of March 27, 2021, Vaxzevria is approved in ≥70 countries and, in all of the countries, is indicated for the prevention of COVID-19 in people aged ≥18 years, including the elderly aged ≥65 years. Also, Vaxzevria is authorized for emergency use by WHO in order to acquire active immunity to prevent COVID-19 in adults aged ≥18 years, including the elderly aged ≥65 years. In US, a large-scale (≥30,000 participants) clinical study including the elderly aged ≥65 years is ongoing, in which ≥23% of participants are aged ≥65 years.

As discussed in Sections 7.R.2.2.3 and 7.R.3.3.2, based on the efficacy and safety data from the pooled analysis and Japanese Study D8111C00002, as well as the foreign post-marketing safety information, Vaxzevria is expected to have efficacy also in the elderly, and its safety is also acceptable. Elderly people have a particularly high risk of severe COVID-19. In the current COVID-19 emergency, Vaxzevria can achieve the public health purpose of reducing the risk of being affected by COVID-19 in elderly people.

PMDA's view:
As discussed in Section 7.R.2.2.3, the efficacy of Vaxzevria is expected also in the elderly. In addition, as examined in Section 7.R.3.3.2, the safety profile in the elderly was not largely different from that in other populations, and the incidence of AEs in the elderly was low. Therefore, there are no events that require further caution in the elderly compared with the non-elderly. The elderly aged ≥65 years is considered to be a risk factor for severe COVID-19 (The Clinical Guidance for COVID-19 [Version 4.2]) and these people are prioritized for vaccination in Japan. Since the prevention of COVID-19 in these people is important, the need for Vaxzevria is high.

7.R.4.2.3 Pregnant or lactating women

Pregnant or lactating women were excluded from the clinical studies of Vaxzevria. The safety in pregnancy and pregnant women during clinical studies is described in Section 7.R.3.3.3.

The applicant's explanation about the vaccination with Vaxzevria in pregnant or lactating women:
Since data of Vaxzevria in pregnant women are limited, the following precaution will be provided: "Vaxzevria should be administered to pregnant women or women who may be pregnant only when the benefits of vaccination to mother and fetus outweigh the possible risks associated with vaccination." Since no particular concerns have been noted in the reproductive and developmental toxicity studies of Vaxzevria (see Section 5.5), Vaxzevria can be administered to pregnant women if the benefits of vaccination outweigh the possible risks. In addition, since no data are available on Vaxzevria in lactating women, the following precaution will be provided "Continuation or discontinuation of breastfeeding should be considered while taking into account the benefits of vaccination as well as the benefits of breastfeeding."

On the basis of the review in Section 7.R.3.3.3 together, PMDA accepted the applicant's explanation.

7.R.4.2.4 Seropositive individuals including previously infected individuals

The applicant's explanation:

In the results of pooled analysis, the number of participants with COVID-19 occurring ≥15 days after the second dose in the efficacy analysis seropositive subgroup was 0 of 264 participants in the Vaxzevria group and 3 of 284 participants in the control group in the SDSD + LDSD subgroup and 0 of 246 participants in the Vaxzevria group and 2 of 271 participants in the control group in the SDSD subgroup. As for safety, the number of participants who were seropositive at baseline (366 in the Vaxzevria group and 387 in the control group) was limited. However, no clinically significant differences were observed in the onset profile of adverse reactions or the profile or severity of unsolicited AEs between subgroups by baseline serostatus. Also, there were no clinically meaningful imbalances in the incidence of SAEs or AESIs by baseline serostatus between the Vaxzevria and control groups.

The results of primary analysis (DCO2) of the pooled analysis revealed that participants in the seropositive subgroup had a high level of humoral immunity prior to vaccination, but showed a substantial induction of neutralizing antibodies after vaccination with Vaxzevria (Table 51).

Table 51 Neutralizing Antibody Titers against SARS-CoV-2 in the Pooled Analysis (Neutralizing Antibody Assay Using Pseudovirus) (Immunogenicity Analysis Set, DCO2)

Baseline serostatus	Timing of assay		SDSD + LDSD		SDSD
			Vaxzevria	Control	Vaxzevria
		N	2122	1569	1746
Negative	28 days after the first dose	n/N_{sub}	801/2079	684/1536	652/1706
		GMT	**60.081**	**20.817**	**61.266**
		[2-sided 95% CI]	[54.91, 65.74]	[20.25, 21.39]	[55.46, 67.68]
	28 days after the second dose	n/N_{sub}	834/2079	683/1536	676/1706
		GMT	**180.881**	**21.721**	**174.773**
		[2-sided 95% CI]	[167.07, 195.83]	[20.93, 22.55]	[159.73, 191.23]
Positive	28 days after the first dose	n/N_{sub}	26/43	25/33	25/40
		GMT	**1484.921**	**122.801**	**1473.330**
		[2-sided 95% CI]	[959.00, 2299.27]	[72.66, 207.54]	[934.07, 2323.93]
	28 days after the second dose	n/N_{sub}	26/43	21/33	25/40
		GMT	**1004.487**	**124.464**	**1026.915**
		[2-sided 95% CI]	[648.43, 1556.05]	[69.87, 221.73]	[652.15, 1617.04]

N = number of participants per subgroup; n = number of participants evaluated

Vaxzevria can induce immunoreaction in vaccine recipients who already have a high antibody titer against SARS-CoV-2. This finding is important considering the following situation: (a) SARS-CoV-2 infection rate is increasing. (b) The serum epidemiological study showed >16% of high-risk populations (e.g., healthcare professionals and urban residents) were seropositive for SARS-CoV-2, and this seropositive rate is expected to continue to increase until a large-scale vaccination is conducted (*JAMA.* 2020; 9:893-5).

The enhancement of immunogenicity after 2 doses of Vaxzevria has been demonstrated. Therefore, in the 4 studies included in the pooled analysis, participants who had a virologically-confirmed SARS-CoV-2 infection after the first dose were allowed to receive the second dose, to ensure the potential immunological benefit of the second dose. According to the protocols of the studies, participants who developed COVID-19 or tested positive for asymptomatic SARS-CoV-2 infection before the second dose were also allowed to receive the second dose of the assigned study vaccine after a certain period of time. In the pooled analysis, the proportion of participants

who was seronegative at baseline and had SARS-CoV-2 virologically confirmed COVID-19 before receiving the second dose of study vaccine, was <1% of all participants (89 of 11,319 in the Vaxzevria group and 102 of 11,291 in the control group), and no participants were reinfected with SARS-CoV-2 after the second dose.

PMDA's view:
It is unnecessary to exclude seropositive individuals, including those who were previously infected, from the target populations for vaccination for the following reasons: (1) No safety concerns have been observed in the participant group who are seropositive at baseline compared with the seronegative group at baseline; and (2) it is not feasible to check the serostatus of a potential vaccine recipient before vaccination with Vaxzevria in clinical settings.

7.R.4.2.5 Children

The clinical data package for the present application does not include the results of clinical studies in children.
The applicant's explanation about the status of pediatric use of Vaxzevria in foreign countries:
The pediatric indication of Vaxzevria has not been approved in any country, and the number of vaccinated children in the post-marketing setting overseas is unknown. However, 534 AEs have been reported in children aged <18 years as spontaneous reports in the foreign post-marketing setting. These events were considered to be associated with off-label use, and the major adverse reactions reported were consistent with those reported in adults. Table 52 shows the details of adverse reactions with ≥5 episodes reported in children.

Table 52 Adverse Reactions (PT) with ≥5 Episodes in Children Aged <18 Years in the Foreign Post-marketing Setting (Period: January 1, 2021 - February 28, 2021)

SOC	PT (MedDRA/J Ver. 23.1)	Number of adverse reactions	Number of children experiencing serious adverse reactions
Gastrointestinal disorders	Abdominal pain upper	5	5
	Diarrhoea	16	8
	Nausea	27	16
	Vomiting	9	5
General disorders and administration site conditions	Adverse drug reaction	6	3
	Chills	48	32
	Fatigue	29	15
	Illness	6	4
	Influenza like illness	10	6
	Malaise	9	3
	Pain	12	6
	Pyrexia	59	24
Infections and infestations	Influenza	5	2
Musculoskeletal and connective tissue disorders	Arthralgia	13	7
	Myalgia	16	11
	Pain in extremity	10	3
Nervous system disorders	Dizziness	13	8
	Headache	67	35
	Paraesthesia	7	3
	Tremor	10	5
Respiratory, thoracic and mediastinal disorders	Cough	6	1
	Dyspnoea	8	3
Skin and subcutaneous tissue disorders	Hyperhidrosis	10	4
Vascular disorders	Peripheral coldness	5	3

Currently, the global development is in progress aiming to start enrollment of children aged 0 to 18 years into the study in [redacted] 20[redacted]. In Japan as well, as soon as the dosage and administration for adults are determined, the discussion of Vaxzevria development for children will be started. The University of Oxford has started a clinical study to evaluate the safety and immune response of vaccination with Vaxzevria in children aged 6 to 18 years.

PMDA's view:

The infection status of SARS-CoV-2 in children in Japan has been reported by the Japan Pediatric Society and the Japanese Society for Kawasaki Disease. According to the report, COVID-19 is relatively mild and does not require treatment in many cases. As of February 23, 2021 in Japan, approximately 10,000 children aged <10 years and approximately 20,000 individuals in their 10s had COVID-19 with no reports of deaths, and that although a small number of children had severe COVID-19, all of them recovered with treatment ("Serious pediatric cases of COVID-19" [in Japanese] published by the Japan Pediatric Society and the Japanese Society for Kawasaki Disease, http://www.jpeds.or.jp/modules/guidelines/index.php?content_id = 129 [last accessed on April 6, 2021]). Since no clinical study data are currently available on the efficacy and safety of vaccination with Vaxzevria in children aged <18 years, vaccination with Vaxzevria should not be proactively recommended for this age group at this point. However, a pediatric clinical study should be conducted to investigate the efficacy and safety of Vaxzevria in children because some children, albite a small number, had severe COVID-19 as described above.

7.R.4.2.6 Individuals who previously used adenoviral vector products including Vaxzevria (e.g., vaccines, gene therapy products)

[1] Effect of anti-ChAdOx1 vector immunity at the second dose of Vaxzevria on the immunity against SARS-CoV-2 antigen

The applicant's explanation:
In Study COV001, the mean (range) of anti-ChAdOx1 vector neutralizing antibody titer of the vaccine recipients (n = 10) who received 2 doses of Vaxzevria at a dose interval of 4 weeks was 506 (321, 1246) at 28 days after the first dose and 432 (181, 622) at 28 days after the second dose, showing no increase in anti-ChAdOx1 vector neutralizing antibody titer after the second dose. In addition, the correlation between anti-ChAdOx1 vector neutralizing antibody titer and anti-S protein antibody titer or S protein-specific T cell response at 28 days after the second dose was analyzed. The results suggested that immune response to SARS-CoV-2 antigen after the second dose is hardly affected by the anti-ChAdOx1 vector immunity. In the future, anti-ChAdOx1 vector neutralizing antibodies will be analyzed also in the immunogenicity analysis set of the pooled analysis.

[2] Efficacy and safety of Vaxzevria in individuals who previously used adenoviral vector products except Vaxzevria (e.g., vaccines, gene therapy products)

The applicant's explanation:
In clinical studies included in the clinical data package of Vaxzevria (except Study COV002), participants who had previously received adenovirus vector vaccines were excluded. The pooled analysis also excluded participants in the group who had previously received ChAdOx1 vector vaccines (Group 11 of Study COV002). Even with the results of the pooled analysis, therefore, the efficacy and safety of Vaxzevria is unknown in individuals who have previously received other ChAdOx1 vector vaccines or other adenoviral vector products.

On the other hand, Study COV002 assessed the impact of anti-ChAdOx1 vector immunity on the immune response to SARS-CoV-2 antigen by establishing a cohort (Group 11) specific to participants who had previously received ChAdOx1 vector vaccines except Vaxzevria. Anti-S protein antibody titers (GMT [95% CI]) at 28 days after the first dose of Vaxzevria was 132.1 (54.55, 319.9) in participants in Group 11 and 214.10 (156.26, 293.36) in participants aged 18 to 55 years with no prior vaccination with ChAdOx1 vector vaccines; participants in Group 11 had slightly lower anti-S protein antibody titers. However, the anti-S protein antibody titer at 28 days after the second dose of Vaxzevria at a 4-week dose interval (GMT [95% CI]) was similar: 679.5 (399.4, 1156) in the former group and 627.88 (475.82, 828.53) in the latter group.

These results suggested that vaccination with 2 doses of Vaxzevria would be minimally affected by pre-existing anti-ChAdOx1 vector immunity. Therefore, Vaxzevria can be administered to individuals who have previously received ChAdOx1 vector vaccines other than Vaxzevria.

PMDA's view:
An increase in the neutralizing antibody titer against SARS-CoV-2 after the second dose led to a booster effect in the immunogenicity analysis set (see Section 7.R.2.2.1.2). Given this finding, together with the applicant's explanation, anti-ChAdOx1 vector immunity is considered to have only a limited effect on the immune response against the S protein after the second dose. However, only limited information is available on the effect of anti-ChAdOx1 vector immunity on the efficacy, immunogenicity, and safety of Vaxzevria. In addition, there has been almost no experience of vaccination with Vaxzevria in individuals who have previously used adenovirus vector products other than Vaxzevria. Considering these facts, the applicant should continuously collect

information in the post-marketing setting, and if any new findings become available, the applicant should take appropriate measures, such as examining the necessity of additional precautions.

7.R.5 Indication

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

PMDA's view:

The pooled analysis demonstrated the efficacy of Vaxzevria against COVID-19, and the Japanese Study D8111C00002 confirmed an increase in serum neutralizing antibody titers equivalent to the level in the pooled analysis. Therefore, Vaxzevria is expected to have similar efficacy against COVID-19 in the Japanese population (see Section 7.R.2) and Vaxzevria has tolerable safety profile (see Section 7.R.3). Therefore, based on the description in "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2" and the indications, etc. of the approved SARS-CoV-2 vaccines and other vaccines for prevention of infections, the indication of Vaxzevria should be "prevention of disease caused by SARS-CoV-2 infection (COVID-19)," as proposed by the applicant.

7.R.6 Dosage and administration

The proposed dosage and administration was as follows: "The usual adult dosage is 2 separate doses of 0.5 mL each administered intramuscularly at a 4- to 12-week interval."

PMDA's view:

As a result of the review presented below, the appropriate dosage and administration for Vaxzevria is "Two separate doses of 0.5 mL each should be administered intramuscularly at a 4- to 12-week interval." Furthermore, the Precautions Concerning Dosage and Administration section should include a precautionary statement to the effect that "Vaxzevria should be administered at an interval of ≥8 weeks to achieve the maximum efficacy."

The dosage and administration of Vaxzevria will be finalized by taking account of comments raised in the Expert Discussion and preliminary results from the ongoing US Study D8110C00001.

7.R.6.1 Dosage and number of doses

The applicant's explanation about the dosage and number of doses of Vaxzevria:

In the clinical studies of Vaxzevria, the dosage was selected on the basis of the following results from clinical experience with the ChAdOx1 adenovirus vector vaccines expressing different transgenes and other similar adenovirus vectored vaccines (e.g., ChAd63).

- A Phase I study of a the ChAdOx1-vectored vaccine expressing the full-length S protein from a related betacoronavirus, MERS-CoV, evaluated 3 dose levels (5×10^9 vp, 2.5×10^{10} vp, and 5×10^{10} vp). After a single dose, all dose levels were well tolerated, and IgG responses increased across all groups, peaking approximately 28 days post vaccination (*Lancet Infect Dis.* 2020;20:816-26). Neutralizing antibodies increased at the 5×10^{10} vp dose level, while no significant increase in neutralizing antibodies from baseline

was seen at the lower dose levels.

- According to data on ChAdox1 vectors expressing other transgenes produced by the same platform technology, the dose of 5×10^{10} vp produces high immunogenicity (*PloS One.* 2012:7:e40385, *Vaccine.* 2009;27:3501-4, etc.).
- A heterologous vaccine given as a booster dose after the first dose is known to increase the immune responses to adenovirus vectors (Zabdeno: EPAR-Public assessment report. EMA/323670/2020.28 May 2020.1). However, 2 doses of an adenovirus type 5 Ebola vaccine (i.e., 2 doses of a homologous vaccine) also enhanced both cellular and humoral immunity, and the antibody geometric mean titers after the second dose was approximately 9 times those after the first dose (*Lancet Glob Health.* 2017;5:e324-34).

Furthermore, in the 4 studies included in the pooled analysis, immunogenicity was enhanced after the second dose of Vaxzevria (at a 4-week interval) in Group 3 of the preceding Study COV001 (*Nat Med.* 2021;27:279-88, *Lancet.* 2020;396:466-78); therefore, it was decided that 2 doses would be given in the entire program.

PMDA's view:

The efficacy of Vaxzevria was demonstrated in the SDSD + LDSD Seronegative for Efficacy Analysis Set, the primary analysis population in the pooled analysis, and similar results were demonstrated in the SDSD Seronegative for Efficacy Analysis Set (see Section 7.R.2.2.1). Since there was no major problem in handling the SDSD regimen and the LDSD regimen in the same manner for the primary analysis (see Section 7.R.2.2.1.2), the dosage and administration of "2 separate doses of 5×10^{10} vp each (SD)" is appropriate.

The LD (2 to 2.5×10^{10} vp) should not be included in the dosage and administration, because the pooled analysis was not planned to demonstrate the efficacy of the LD and the efficacy evaluation in the subgroup receiving LDSD was positioned as an exploratory analysis.

7.R.6.2 Dose interval

The applicant's explanation about the 4- to 12-week dose interval:

The interval between the 2 doses specified in the protocols of studies included in the pooled analysis varied from 4 to 12 weeks among studies and dosing regimens. The effect of dose interval on immunogenicity and efficacy was assessed based on the results of the interim analysis (DCO1) and primary analysis (DCO2). The results showed efficacy with an interval of ≥4 weeks between doses. In addition, there was a trend toward higher neutralizing antibody titers after the second dose with longer dose intervals within the range of 4 to 12 weeks (see Section 7.R.2.2.2). No particular safety concern has been noted in the pooled analysis results (see Section 7.R.3.1.3). In view of the above, "2 intramuscular doses at an interval of 4 to 12 weeks" is considered appropriate.

Both in UK (where the temporary authorization of emergency supply of Vaxzevria is granted) and in EU (where the conditional marketing authorization is granted), the recommended dose interval of Vaxzevria is "4 to 12 weeks." WHO recommends the dose interval of "8 to 12 weeks" for Vaxzevria (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-

background-2021.1 [last accessed on April 6, 2021]), which is provably based on vaccine efficacy in the SDSD Seronegative for Efficacy Analysis Set at the primary analysis (DCO2). In addition, WHO recommended this dose interval probably because vaccine supply is limited in some countries and therefore a longer interval allows more people to receive the first dose in countries with limited vaccine supply.

PMDA asked the applicant to explain the following points regarding the studies included in the clinical data package for Vaxzevria: (a) The dose intervals after the first dose (acceptable period) specified for each group in the protocol, and the rationale for the dose intervals. (b) Target sample size for each group and the number of participants actually included in the efficacy analysis. (c) The distribution of dose intervals actually employed in the studies included in the pooled analysis.

The applicant's response:
Table 53 shows the prespecified dose intervals after the first dose by group, target sample size, and the number of participants included in the efficacy analysis set by group.

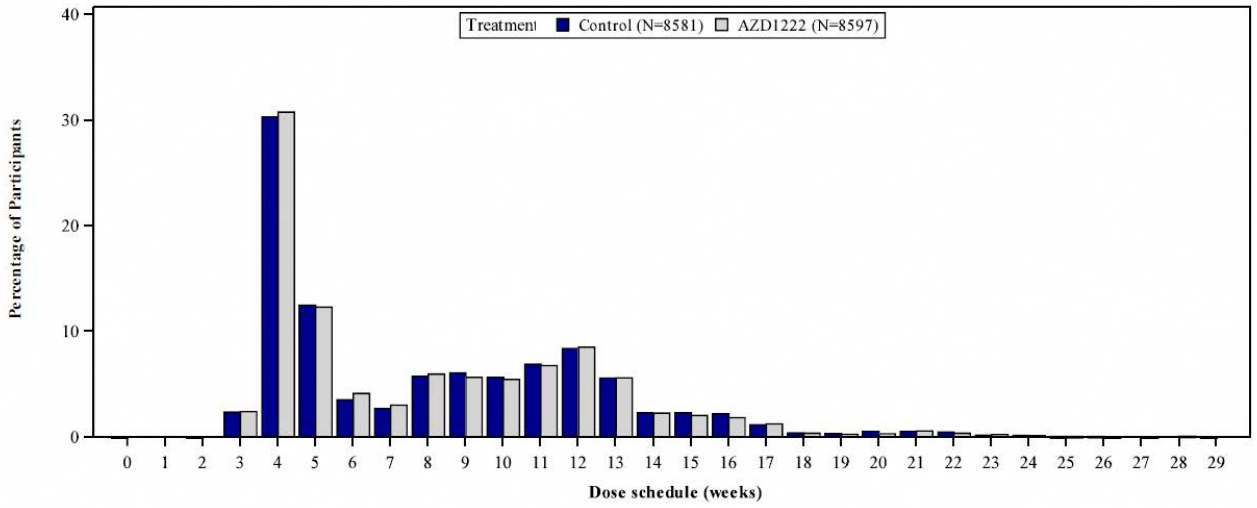
The initially planned dosage was a single dose of Vaxzevria, but the enhancement of immunogenicity was observed after the second dose (at a 4-week interval) in the monkey challenge study (see Section 3.1.3) and in Group 3 of Study COV001 (see Section 7.R.6.1); therefore, the plan was changed to administer 2 doses in the entire program. The longer dose interval increases the maturity of immunity as seen with hepatitis A virus vaccines, etc., but many prophylactic vaccines for infections are given at an interval of 4 weeks. Further, a vaccination method that can promptly induce immunity should be employed in the event of a global pandemic. The applicant therefore intended to define the standard dose interval as 4 weeks between the first and second doses unless there are logistical restrictions. The dose interval of "4 weeks" was thus used in Study COV002 (some groups) and Study COV005, etc.

In the study groups that started to receive the study vaccine earlier, the second dose could not often be administered at a 4-week interval, due to a delay in the decision to introduce the second dose and a delay in the supply of the vaccine products because of logistical constraints. Therefore, the dose interval was defined based on the feasibility in view of the supply status and distribution problems of the vaccine products.

Table 53 Prespecified Dose Intervals after the First Dose by Group in the Studies Included in the Pooled Analysis (Studies COV001, COV002, COV003, and COV005) and Japanese Study D8111C00002

Study	Protocol-specified dose interval (acceptable range)	Group (SDSD + LDSD Efficacy Analysis Set only, including control group)	Planned number of participants (Total)	Number of participants in analysis population in the pooled analysis (SDSD + LDSD Efficacy Analysis Set)
COV001	8 weeks (7-10 weeks)	2c, 2e	Up to 30	17
	≥4 weeks	2f, 2g, 4c, 4d	Up to 930	724
COV002	4 weeks (4-6 weeks)	9-a1, a2, 10-a1, a2	2000	1592
	≥4 weeks	4-c1, c2, 6-b1, b2	Up to 9450	6615
COV003	4-12 weeks (4-14 weeks)	1c, 1d	Up to 10300	6753
COV005	4 weeks (3-5 weeks)	1, 2a, 2b	1970	1477
Japanese Study D8111C00002	4 weeks (±2 days)	All	256	-

Figure 4 shows the dose intervals actually employed in the studies included in the SDSD + LDSD Seronegative for Efficacy Analysis Set, the efficacy analysis population in the pooled analysis.



Number of Subjects

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Control: n=	1	0	1	201	2599	1069	302	230	491	519	484	591	718	478	196	195	186	100	32	27	44	45	38	14	12	3	4	0	0	1
AZD1222: n=	0	0	0	206	2644	1055	354	259	511	484	466	580	730	480	194	175	157	106	30	21	26	49	30	20	9	3	2	1	5	0

Percentage

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Control:	0.01	0	0.01	2.34	30.29	12.46	3.52	2.68	5.72	6.05	5.64	6.89	8.37	5.57	2.28	2.27	2.17	1.17	0.37	0.31	0.51	0.52	0.44	0.16	0.14	0.03	0.05	0	0	0.01
AZD1222:	0	0	0	2.40	30.75	12.27	4.12	3.01	5.94	5.63	5.42	6.75	8.49	5.58	2.26	2.04	1.83	1.23	0.35	0.24	0.30	0.57	0.35	0.23	0.10	0.03	0.02	0.01	0.06	0

Figure 4 Number of Participants by Dose Interval in the Pooled Analysis Population (Studies COV001, COV002, COV003, and COV005) in Primary Analysis (DCO2) (SDSD + LDSD Seronegative for Efficacy Analysis Set)

PMDA asked the applicant to explain the reason for defining the maximum dose interval as 12 weeks in the proposed dosage and administration.

The applicant's explanation:

The maximum dose interval was defined as 12 weeks because 2 doses of Vaxzevria administered at a 4- to 12-week interval were shown to have reliable vaccine efficacy, and because only limited information was available on dose intervals exceeding 12 weeks.

Results of the interim analysis (DCO1), the primary efficacy analysis of the pooled analysis, showed that vaccine efficacy (2-sided 95.84% CI) at ≥15 days after the second dose was 70.42% [54.84, 80.6] in participants who were seronegative at baseline and received 2 doses (SDSD or LDSD), demonstrating the preventive effect of Vaxzevria against COVID-19. The results of this analysis were supported by similar vaccine efficacy observed in the group receiving 2 SD doses (SDSD) (62.10%) and in the SDSD + LDSD Seronegative ITT for Efficacy population (69.13%). In addition, vaccine efficacy (2-sided 95% CI) in the analysis of the SDSD Seronegative for Efficacy Analysis Set with the dose interval of 4-12 weeks was 60.86 (36.61, 75.84), which was consistent with the above data.

An exploratory analysis of the effect of dose interval on vaccine efficacy in the SDSD + LDSD Seronegative for Efficacy Analysis Set (DCO1) suggested that an interval of >12 weeks is associated with a lower estimated robustness of vaccine efficacy. In this analysis, 1000 bootstrapping interactions (random sampling with replacement) were performed in participants whose dose interval is equal to or more than the number of days for each day from 30 days to 100 days of dose interval, and vaccine efficacy and its CI were derived from the extracted samples (Figure 5). After approximately 12 weeks post dose, the number of participants substantially decreased, resulting in a very wide CI. Therefore, at present, there are not sufficient data to justify the dose interval exceeding 12 weeks.

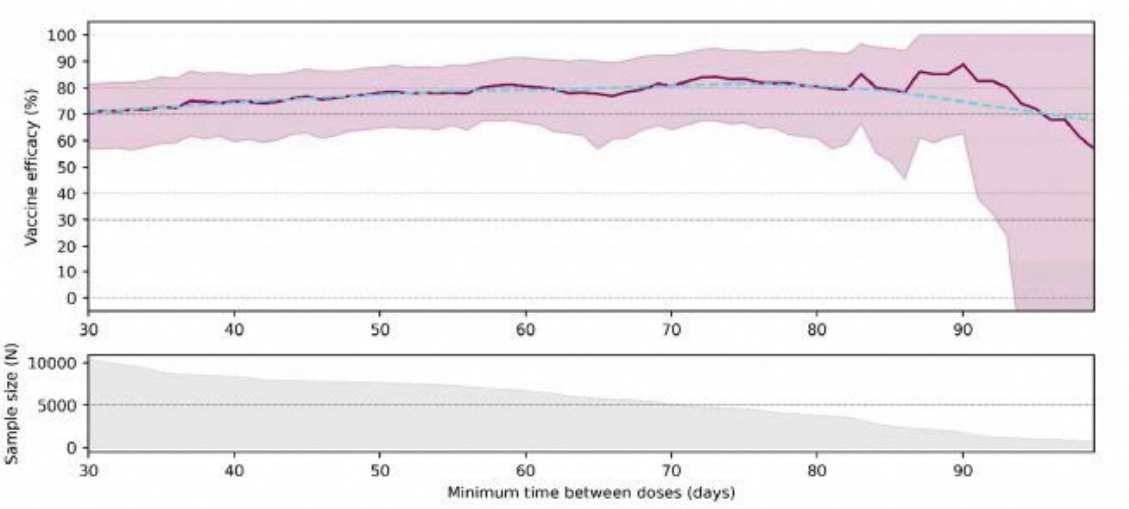


Figure 5 Exploratory Analysis of Median Vaccine Efficacy for Dose Interval (SDSD + LDSD Seronegative for Efficacy Analysis Set, DCO1)
Solid line, individual values of median vaccine efficacy; dashed line, a smoothed version of the median line; shaded area, empirical 95% CI

Confirmed COVID-19 occurring between ≥22 days post first dose and the second dose of the study vaccine were exploratively analyzed in the Dose 1 SD Seronegative Efficacy for Analysis Set. The follow-up period was from 22 days post first dose to the second dose. Participants who did not receive the second dose were censored at the time of data cutoff, study discontinuation, or onset of COVID-19. Table 54 shows the vaccine efficacy ≥22 days post first dose and before the second dose; it was comparable to the vaccine efficacy [2-sided 95% CI] (63.09% [51.81, 71.73]) after the completion of 2 doses (SDSD) of Vaxzevria (DCO2).

Table 54 Vaccine Efficacy Based on Confirmed COVID-19 Occurring between ≥22 Days Post First Dose and the Second Dose (Dose 1 SD Seronegative Efficacy for Analysis Set, DCO2)

	Vaxzevria	Control
Number of participants	9335	9312
Number of events (%)	32 (0.34)	82 (0.88)
VE [2-sided 95% CI][*1]	60.99 [41.37, 74.05]	

*1: Poisson regression model with study identifier, vaccine group, and age at screening (18 to 55, 56 to 69, and 70 years) as factors, as well as the log of the follow-up period as an offset

Based on the above, it was considered possible to administer the second dose after a 4- to 12-week interval.

PMDA's view:

In the development of Vaxzevria, multiple clinical studies were simultaneously conducted under a pandemic situation, and the study plans including the dosage of Vaxzevria were changed as needed based on the information obtained. In addition, there were also limitations related to the supply and distribution of the vaccine products, resulting in widely varying dose intervals (3 to 28 weeks) in the efficacy analysis population in the pooled analysis. The applicant and the University of Oxford originally assumed the 4-week interval for the 2 doses of Vaxzevria, but a pooled analysis suggested that vaccine efficacy of Vaxzevria may increase with longer dose intervals in individuals receiving 2 doses at a ≥4-week interval. Normally, a study should have been designed and conducted to demonstrate the efficacy of Vaxzevria at a more optimized dose interval; however, given the above-mentioned limitations associated with the drug development under the pandemic, it is inevitable that the above policy was taken for the conduct of a series of clinical studies included in the pooled analysis.

The pooled analysis includes data from participants who received Vaxzevria at various dose intervals as mentioned above, but approximately 82% of participants on Vaxzevria received the doses at an interval of 4 to 12 weeks (Figure 4). Furthermore, the efficacy of Vaxzevria has been suggested in both the subgroups of participants vaccinated at an interval of (a) 4 to 8 weeks and (b) 9 to 12 weeks (see Section 7.R.2.2.2) as well as in the SDSD + LDSD Seronegative for Efficacy Analysis Set, the primary efficacy analysis set. Vaxzevria administered at a 4-week interval to Japanese participants in Japanese Study D8111C00002 resulted in neutralizing antibody titers similar to those in the subgroups of participants receiving Vaxzevria at an interval of 4 to 8 weeks in the pooled analysis (see Section 7.R.2.2.1.3). There has been no major concern about the safety and tolerability in the population receiving Vaxzevria at an interval of 4 to 12 weeks compared with the overall population (see Section 7.R.3.1.3 [3]). Based on these findings, the interval of "4 to 12 weeks," (the maximum of 12 weeks) is acceptable. Because immunity should be induced as soon as possible under the current pandemic situation, the dose interval should not exceed 12 weeks. Two doses of Vaxzevria should therefore be administered at the interval specified in the Dosage and Administration section.

The neutralizing antibody titer in Japanese Study D8111C00002 was comparable to that in the subgroups of 4- to 8-week dose intervals in the pooled analysis. In contrast, the pooled analysis, albeit exploratory data, suggested a trend toward higher vaccine efficacy with longer dose intervals in the subgroup analysis of vaccine efficacy by dose interval, and a similar trend was observed in neutralizing antibody titers (see Section 7.R.2.2.2). Based on these, in order to obtain the maximum efficacy of Vaxzevria, 2 doses of Vaxzevria should be administered at an interval of ≥8 weeks and ≤12 weeks.

7.R.6.3 Target age groups for vaccination

PMDA' view on the target age groups for Vaxzevria:

The ages of participants enrolled in clinical studies included in the clinical data package of Vaxzevria were ≥18 years old for Japanese Study D8111C00002, 18 to 55 years for Study COV001, ≥18 years for Study COV002, ≥18 years for Study COV003, and 18 to 65 years for Study COV005. Although the studies enrolled only a limited number of adults 55 to 65 years old and elderly participants ≥65 years old, the target age groups for Vaxzevria should be ≥18 years old based on the data examined in Sections 7.R.2.2.3, 7.R.3.3.2, and 7.R.4.2.2.

Therefore, the following statement should be included in the Precautions Concerning Dosage and Administration section to define the target populations for vaccination: "Vaxzevria should be administered to people ≥18 years old."

7.R.7 Post-marketing investigations

The applicant's explanation about post-marketing surveillance for Vaxzevria:

Only limited information is available about the safety of Vaxzevria (including long-term safety data) in Japanese participants before marketing approval (see Section 7.R.3). Therefore, a general use-results survey will be conducted to investigate the safety of Vaxzevria for up to 12 months after the last dose of Vaxzevria. The survey will include all participants who give consent to participate in the 12-month observation after the last dose of Vaxzevria, among participants in the "Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan" (Emerging and Re-emerging Infectious Diseases and Vaccination Policy Promotion Research Project funded by the FY 2020 Health and Labour Policy Promotion Survey Grant; planned sample size, 10,000 to 20,000 individuals each for vaccines to be surveyed). Shock/anaphylaxis, immune-mediated neurological reactions, and vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD), will be included in the safety specification. The planned observation period is 11 months: from the following day of 28 days after the last dose of Vaxzevria (the last date of the follow-up period in the preceding cohort survey) to 12 months after the last dose.

In addition, a specified use-results survey (observation period: from the day of the first dose [Day 1] to 28 days after the last dose) will be conducted to investigate the safety of Vaxzevria in the elderly and individuals with underlying diseases who are at high risk of severe COVID-19, because no sufficient safety data in these populations have been obtained from clinical studies of Vaxzevria (see Sections 7.R.3.3.1 and 7.R.4.2.1). Because individuals at high risk of severe COVID-19 are expected to receive Vaxzevria during a limited period, the planned sample size is 1000 individuals (as the safety analysis set) considering the feasibility of the survey. The survey will enroll a certain number of elderly people who are at particularly high risk of severe COVID-19 (see Section 7.R.4.2.2).

In addition to the above survey, the long-term safety of Vaxzevria will be investigated based on the information obtained from the post-marketing clinical study (the extension of Japanese Study D8111C00002) and the follow-up of Studies COV001, COV002, COV003, COV005, and D8110C00001.

In order to promote the proper use of Vaxzevria and ensure its safety, the applicant plans to periodically prepare a list of reported adverse reactions to Vaxzevria and to provide it to healthcare professionals as an additional risk minimization activity.

PMDA's view:
Since thrombotic, thromboembolic and neurovascular events have been reported after vaccination with Vaxzevria (see Section 7.R.3.3), these events should also be included in the safety specification and the incidences of the events should be monitored in post-marketing surveillance. In addition, since the target population to be vaccinated with Vaxzevria may change according to the progress of vaccination with already-approved SARS-CoV-2 vaccines, it is necessary to confirm the population to be vaccinated with Vaxzevria at the start of the survey and reconsider the details of the post-marketing surveillance plan as appropriate.

PMDA will reach a final conclusion on the post-marketing investigations based on comments raised in the Expert Discussion.

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

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

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

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

The inspection is currently underway, and the results and PMDA's conclusion will be reported in Report (2).

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

The inspection is currently underway, and the results and PMDA's conclusion will be reported in Report (2).

10. Overall Evaluation at the Time of Preparation of the Report on Special Approval for Emergency (1)

On the basis of the submitted data, PMDA has concluded that Vaxzevria has efficacy in the prevention of COVID-19 and that Vaxzevria has acceptable safety in view of its benefits. In the current situation where prompt supply of multiple types of vaccines to prevent COVID-19 is required, making Vaxzevria available in clinical practice is meaningful. PMDA also considers that it is necessary to further investigate the dosage and administration, contents of precautions in the package insert, post-marketing investigation issues, etc.

PMDA considers that Vaxzevria may be approved if the product is not considered to have any particular problems based on comments from the Expert Discussion.

11. Other

11.1 Vaccine Products and Dose Levels of Vaxzevria Used in Clinical Studies

Table 55 shows the vaccine products and dose levels of Vaxzevria used in clinical studies listed in Table 15 in Section 7.

Table 55 Vaccine Products and Dose Levels of Vaxzevria Used in Clinical Studies

Vaccine product/dose level of Vaxzevria	SD/LD	Study/group or cohort
2.2×10^{10} vp (qPCR) [redacted] product[a)]	LD	Study COV002, Groups 1, 2, and 4
2.5×10^{10} vp (qPCR) [redacted] product[b)]	LD	Study COV001, Group 2d
3.5 to 6.5×10^{10} vp [redacted] product[c)]	SD	Study COV001, Groups 2f, 4c, and 4d Study COV002, Groups 1a3, 2a3, 4c1, 4c2, 5a3, 5d1, 6b1, 7b1, 8b1, 9a1, 9a2, 10a1, and 11 Study COV003, Groups 1a and 1c Study COV005, Groups 2b and 3 Study D8111C00002, Cohorts C and D
5×10^{10} vp (Abs260) [redacted] product[d)]	LD	Study COV002, Groups 1a3, 1b1, 2a1, 2a3, 2b1, 4a1, 4b1, 4b2, 4c1, 5a1, and 5a3
5×10^{10} vp (qPCR) [redacted] product[e)]	SD	Study COV001, Group 2c Study COV002, Groups 4c1, 5b1, 5c1, 6a1, 6b1, 7a1, 7b1, 8a1, and 8b1 Study COV003, Groups 1a and 1c Study COV005, Groups 1, 2a, 2b and 3
5×10^{10} vp [redacted] product[f)]	SD	Study COV005, Groups 1, 2a, 2b and 3
5×10^{10} vp [redacted] product[g)]	SD	Study COV001, Groups 1a, 2a, 2c, 2d, 2f, 3, 4a, 4c, and 4d

a) This dose level was classified as LD because the dose was approximately half of SD (5×10^{10} vp).
b) The 2.5×10^{10} vp (half the SD), classified as LD, was selected to evaluate dose saving options
c) Target clinical dose of SD manufactured by [redacted]. It was prepared as a single dose (3.5 to 6.5×10^{10} vp [± 30% of 5×10^{10} vp]) based on the concentration measured by UV spectrophotometry (Abs260).
d) The planned dose was SD (5×10^{10} vp) measured by UV spectrophotometry (Abs260), but the actual dose was 2.2×10^{10} vp measured by [redacted] qPCR, which was classified as LD (see Section 11.5).
e) This dose was classified as SD because viral particle concentration measured by qPCR was 5×10^{10} vp. As an exception, 44 participants in Study COV005 (part of Groups 2a and 2b) received 2×10^{10} vp due to an overestimation of viral particle concentration; this dose (2×10^{10} vp) was classified as LD (see Section 11.5).
f) This is equivalent to the above 5×10^{10} vp (qPCR) [redacted] product. This dose was administered in Study COV005.
g) This dose was classified as SD because viral particle concentration measured by UV spectrophotometry (Abs260) was 5×10^{10} vp.

11.2 Severity Grading Scale for Adverse Events

Tables 56-1 to 3 show the grading scales for adverse events in Studies COV001, COV002, and COV003 and the foreign pooled analyses. These are modified and summarized versions of the grading scales presented in the U.S. FDA's Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Tables 56-1, 2 and 4 show the grading scales for adverse events in the Japanese studies.

The grading scale for adverse events used in Study COV005 was based on the DAIDS AE Grading Corrected Version 2.1-July 2017.

Table 56-1 Clinical Abnormality: Local Reaction to Injectable Product

Local reaction to injectable product	Reaction scale			
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-threatening (Grade 4)
Pain	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/redness[a),b)]	1-2 inches (2.5-5 cm)	>2-4 inches (5.1-10 cm)	>4 inches (>10 cm)	Necrosis or dermatitis exfoliative
Induration/swelling[a),b)]	1-2 inches (2.5-5 cm)	>2-4 inches (5.1-10 cm)	>4 inches (>10 cm)	Necrosis

a) Local reactions should be measured at the greatest single diameter and recorded as a continuous variable. Reactions with a diameter of <1/4 inch (<0.6 cm) will not be recorded.

b) Whether an event falls under "Grade 4 erythema or induration" should be determined by the participant and study staff at the study site. Grade 4 erythema or induration should thus not be recorded in e-diary by participants alone.

Table 56-2 Clinical Abnormalities: Vital Signs

Vital signs[a)]	Vital signs scale			
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Fever (°C)[b)] (°F)[b)]	37.9-38.4 100.1-101.1	38.5-38.9 101.2-102.0	39.0-40 102.1-104	>40 >104
Tachycardia (beats/minute)	101-115	116-130	>130	Emergency room visit or hospitalization for arrhythmia
Bradycardia (beats/minute)[c)]	50-54	45-49	<45	Emergency room visit or hospitalization for arrhythmia
Hypertension; Systolic (mm Hg)	141-150	151-155	>155	Emergency room visit or hospitalization for malignant hypertension
Hypertension; Diastolic (mm Hg)	91-95	96-100	>100	Emergency room visit or hospitalization for malignant hypertension
Hypotension; Systolic (mm Hg)	85-89	80-84	<80	Emergency room visit or hospitalization for hypotensive shock
Respiratory rate (breaths/minute)	17-20	21-25	>25	Intubation

Note: Vital signs are considered as AEs only if there are clinically relevant changes from baseline.

a) Participants should be at rest for all vital sign measurements.

b) It is not allowed to drink hot or cold beverage or smoke shortly before the measurement.

c) Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Table 56-3 Local and Systemic Adverse Events

Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Transient or mild discomfort (<48 hours); no interference with activity; requires no medical intervention/therapy	Mild to moderate limitation in activity; may need some assistance; requires no or minimal medical intervention/therapy	Marked limitation in activity, always requires some assistance, requires medical intervention/therapy	Emergency room visit or hospitalization required

Table 56-4 Clinical Abnormalities: Systemic Condition

Systemic (General)	Performance status scale			
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 to 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity; requires outpatient IV hydration	Emergency room visit or hospitalization for hypotensive shock
Chills	No interference with activity	Some interference with activity	Severe: Interferes with daily activity	Emergency room visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Severe: Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Severe: Interferes with daily activity	Emergency room visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Severe: Interferes with daily activity	Emergency room visit or hospitalization
Systemic (Illness)				
Any illness or clinical adverse event (as defined by the appropriate regulations)	No interference with activity	No treatment required, but some interference with activity	Interferes with daily activity or requires medical intervention	Emergency room visit or hospitalization

11.3 History of Major Changes to the Protocols of the Four Foreign Studies Included in the Foreign Pooled Analysis

Tables 57 to 60 show major amendments up to the following protocol versions:

- Protocol Version [redacted] ([redacted], 20[redacted]) of Study COV001 (Section 7.1.2, Version [redacted], [redacted], 20[redacted]; date of consent of the first participant, [redacted], 20[redacted])
- Protocol Version [redacted] ([redacted], 20[redacted]) of Study COV002 (Section 7.2.1, Version [redacted], [redacted], 20[redacted]; date of consent of the first participant, [redacted], 20[redacted])
- Protocol Version [redacted] ([redacted], 20[redacted]) of Study COV003 (Section 7.3.1, Version [redacted], [redacted], 20[redacted]; date of consent of the first participant: [redacted], 20[redacted])
- Protocol Version [redacted] ([redacted], 20[redacted]) of Study COV005 (Section 7.1.3, Version [redacted], [redacted], 20[redacted]; date of consent of the first participant: [redacted], 20[redacted]).

Table 57 Major Amendments up to Protocol Version [redacted] (Dated [redacted], 20[redacted]) of Study COV001

	Description of change (Protocol Version No.)	Reason for change
Dosage regimen	(1) Low dose (2.5×10^{10} vp) was introduced as the second dose in Group 3 (Version [redacted], [redacted], 20[redacted]) (2) Acetaminophen prophylaxis was added for some participants in Group 4 (Version [redacted], [redacted], 20[redacted]) (3) The dose level for the second dose in Group 3 was returned to 5×10^{10} vp (Version [redacted], [redacted], 20[redacted]). (4) The second dose was added for some participants in Group 2 (Version [redacted], [redacted], 20[redacted]). (5) The second dose was added for all participants in Groups 2 and 4 (Version [redacted], [redacted], 20[redacted])	(1) To allow for evaluation of a low dose as the second dose. (2) To evaluate the safety, adverse reactions, immunogenicity, and efficacy of Vaxzevria in combination with acetaminophen. (3) To ensure consistency with the second dose in Study COV002. (4) To evaluate the safety and immunogenicity of the second dose in some participants. (5) The interim immunogenicity results in Group 3 indicated that neutralizing antibody titer was improved with 2 doses compared with 1 dose.
Comparator	Saline placebo was replaced with active control (meningococcal vaccine) (Version [redacted], [redacted], 20[redacted])	To minimize the potential for unintentional unblinding of participants and to reduce bias in adverse reactions and safety reporting and/or health-related behaviors of participants in the event of symptomatic COVID-19.
Sample size	(1) Group 4 was added and the number of participants was increased from 500 to 1112 (Version [redacted], [redacted], 20[redacted]) (2) The number of participants was updated to 1090 to reflect actual number of vials available for use (Version [redacted], [redacted], 20[redacted])	(1) More study vaccines could be obtained, and therefore more participants could be enrolled in the active vaccine group. (2) More study vaccines than initially planned could be obtained, which made it possible to increase the number of participants and to shorten the time to interim and primary analyses.
Exclusion criteria	Added: Anosmia and loss of taste prior to enrollment. (Version [redacted], [redacted], 20[redacted])	These symptoms were added, in addition to pyrexia, cough, and shortness of breath, to exclude participants who may have had prior COVID-19 that was not confirmed by laboratory tests.
Primary endpoints	(1) The definition of European Centre for Disease Prevention and Control was applied to the definition of symptomatic patients requiring swab sample test. The scope of events requiring patients to contact the study team was revised to "pyrexia, cough, shortness of breath, or hospitalization for any reason" (Version [redacted], [redacted], 20[redacted]) (2) Lack of smell/taste was added to triggers for swab sample test (Version [redacted], [redacted], 20[redacted]) (3) Modifications to swab sample test (addition of home sample test if symptomatic but negative S0, addition of S3-S5 visit for the second swab sample test) (Version [redacted], [redacted], 20[redacted])	(1) To ensure that suspected cases are subject to tests and assessment. (2) The symptom criteria were revised to correspond to the updated information on symptoms in COVID-19 to ensure that the suspected cases are subject to tests and assessment. Loss of smell/taste was reported as a symptom of COVID-19 several months after the global outbreak; on April 17, 2020, the CDC added "new loss of taste or smell" to the list of symptoms that may appear 2 to 14 days after viral exposure. On May 4, 2020, WHO added "loss of taste or smell" to the list of COVID-19 symptoms in Q&A on the website. (3) To maximize case identification.

Table 58 Major Amendments up to Protocol Version [redacted] (dated [redacted], 20[redacted]) of Study COV002

	Description of change (Protocol Version No.)	Reason for change
Dosage regimen	(1) Prophylactic acetaminophen was introduced to Group 4 (Version [redacted], [redacted], 20[redacted]) (2) Addition of Group 4b: Two doses will be given to up to 100 participants 18 to 55 years old who were originally enrolled in Group 4a (Version [redacted], [redacted], 20[redacted]) (3) The second dose was added to Groups 4 and 6 (Version [redacted], [redacted], 20[redacted]) (4) The second dose was added to Groups 1a, 2a, and 5a (Version [redacted], [redacted], 20[redacted])	(1) To reduce the severity of common local and systemic adverse reactions. (2) To collect immunogenicity data of 2 dose-regimen. (3) (4) The interim immunogenicity results in Group 3 of Study COV001 indicated that neutralizing antibody titer was improved with 2 doses compared with 1 dose.
Group	(1) Group 5 was added (Version [redacted], [redacted], 20[redacted]) (2) The number of participants to be enrolled in Group 4 was reduced (Version [redacted], [redacted], 20[redacted]) (3) Group 6 was added (Version [redacted], [redacted], 20[redacted]) (4) Groups 5a, 5b, and 5c, 7a and 7b, and 8a and 8b were added (Version [redacted], [redacted], 20[redacted]) (5) Group 5d (Batch Comparison group for [redacted] product) was added (Version [redacted], [redacted], 20[redacted]) (6) Groups 9 and 10 (efficacy analysis population of participants ≥56 years old) were added (Version [redacted], [redacted], 20[redacted]) (7) Group 11 was added (Version [redacted], [redacted], 20[redacted]) (8) Group 12 (HIV-positive participants) was added (Version [redacted], [redacted], 20[redacted]) (9) Group 3 was deleted (Version [redacted], [redacted], 20[redacted]) (10) Groups 5e and 5f were added (Version [redacted], [redacted], 20[redacted])	(1) To compare with the vaccine products used in Study COV001. (2) To complete enrollment in Group 4 that used LDSD and establish Group 6 to use SDSD for efficacy evaluation. (3) To compare vaccine products of different manufacturing sites. (4) To evaluate vaccine products of different manufacturing sites (Group 5), collect data from the elderly population, and use the same study designs as those of Groups 1 and 2 (Groups 7 and 8). (5) To compare vaccine products of a new manufacturing site. (6) To evaluate efficacy in participants ≥56 years old. (7) To investigate the safety and immunogenicity in participants who previously received ChAdOx1-vectored vaccine. (8) To investigate the safety and immunogenicity in patients infected with HIV. (9) Another protocol is prepared to evaluate safety and immunogenicity in the pediatric population. (10) To compare batches of vaccine products manufactured by Serum Institute of India in different regimens.
Sample size	(1) Increased from 5,000 to up to 10260 participants (Version [redacted], [redacted], 20[redacted]) (2) Increased the sample size to up to 10560 participants (Version [redacted], [redacted], 20[redacted]) (3) Increased the overall sample size to 12330 participants (Version [redacted], [redacted], 20[redacted]) (4) The number of participants to be enrolled in Groups 9 and 10 was changed to 1000 ± 10% each. No change to the overall sample size (Version [redacted], [redacted], 20[redacted])	(1) Group 5 was added for batch comparison to evaluate differences between vaccine manufacturing sites. The number of participants in Group 4 was increased because more study vaccines than originally planned could be obtained. (2) Batch comparison and elderly groups were newly added to compare adverse reactions and immunogenicity between different dose measurement methods. (3) In response to the addition of a new vaccine manufacturing site, a batch comparison group and efficacy evaluation group of participants ≥56 years old were added. (4) Consideration of enrollment activities at multiple sites and possibility of excessive enrollment.
Inclusion criteria	(1) The upper age limit for enrollment in Groups 4 and 6 was reduced to <56 years old (Version [redacted], [redacted], 20[redacted]) (2) Clarified that participants with prior PCR-positive result can be enrolled in Groups 9, 10, and 11 (Version [redacted], [redacted], 20[redacted])	(1) Because participants ≥56 years old were to be enrolled in Groups 9 and 10. (2) To clarify the inclusion criteria.
Exclusion criteria	(1) Added: Individuals who are seropositive for SARS-CoV-2 prior to enrollment Deleted: New-onset pyrexia, cough, and shortness of breath (Version [redacted], [redacted], 20[redacted]) (2) The following were added to exclusion criteria for the second dose: (a) AEs that may affect participant safety after the first dose or interpretation of study results; and (b) SARS-CoV-2 PCR positivity within 4 weeks (if symptomatic) or 2 weeks (if asymptomatic). (Version [redacted], [redacted], 20[redacted])	(1) This criterion was added instead of an exclusion criterion on risk factors due to the introduction of serology test. (2) To ensure participant safety and interpretability of study results.
Primary endpoints	(1) Lack of smell/taste was added to triggers for swab sample test (Version [redacted], [redacted], 20[redacted]) (2) Nasal/throat swab sample test will be performed only if (a) test is deemed necessary 7 days following the diagnosis of COVID-19 or (b) the initial test is negative. (Version [redacted], [redacted], 20[redacted]) (3) Modification to swab sample test (addition of home sample test if the participant who developed symptoms suspected of COVID-19 tests negative at the initial visit, addition of a visit for the second swab sample test 3 to 5 days after the initial visit) (Version [redacted], [redacted], 20[redacted]) (4) Diagnostic PCR was changed to nucleic acid amplification testing for endpoint definition (Version [redacted], [redacted], 20[redacted])	(1) The symptom criteria were revised to correspond to the updated information on symptoms in COVID-19 to ensure that suspected cases are subject to tests and assessment. Loss of smell/taste was reported as a symptom of COVID-19 several months after the global outbreak; on April 17, 2020, the CDC added “new loss of taste or smell” to the list of symptoms that may appear 2 to 14 days after viral exposure. On May 4, 2020, WHO added “loss of taste or smell” to the list of COVID-19 symptoms in Q&A on the website. (2) (3) To maximize case identification. (4) A broad term was used to include non-PCR-based SARS-CoV-2 diagnostic tests (e.g., transcription mediated amplification [TMA] method).

Table 59 Major Amendments up to Protocol Version [redacted] (dated [redacted], 20[redacted]) of Study COV003

	Description of change (Protocol Version No.)	Reason for change
Dosage regimen	Second dose groups of Groups 1c and 1d were added (Version [redacted], [redacted], 20[redacted])	The interim immunogenicity results in Group 3 of Study COV001 indicated that neutralizing antibody titer was improved with 2 doses compared with 1 dose.
Sample size	(1) Increased from 2000 participants (up to 5000 participants depending on vaccine supply) to up to 10,000 participants (Version [redacted], [redacted], 20[redacted]) (2) Increased to up to 10300 participants (Version [redacted], [redacted], 20[redacted])	(1) To add the elderly cohort and a study site and to include 2 doses. (2) To perform competitive and concurrent enrollment at multiple sites.
Inclusion criteria	Clarified that if the outcome of pregnancy is an abortion or miscarriage, the participant may receive a second dose (Version [redacted], [redacted], 20[redacted])	To clarify the inclusion criteria.
Exclusion criteria	(1) Deleted the requirement for COVID-19 seronegative status prior to enrollment (Version [redacted], [redacted], 20[redacted]) (2) Clarified that a history of COVID-19 can be confirmed by serology test or PCR. (Version [redacted], [redacted], 20[redacted]) (3) The following were added to exclusion criteria for the second dose: (a) AEs that may affect participant safety after the first dose or interpretation of study results and (b) SARS-CoV-2 PCR positivity within 4 weeks (if symptomatic) or 2 weeks (if asymptomatic). (Version [redacted], [redacted], 20[redacted]) (4) Clarified that a history of COVID-19 can also be confirmed by rapid antigen/antibody test (Version [redacted], [redacted], 20[redacted])	(1) The FDA guidelines recommend not to exclude individuals with a history of SARS-CoV-2 infection because of the importance of assessing benefit-risk in those with a history of SARS-CoV-2 infection. In addition, the results of serological test cannot be provided as scheduled due to distribution restrictions at the laboratory. (2) To clarify the inclusion criteria. (3) To ensure participant safety and interpretability of study results. (4) To clarify the inclusion criteria.

Table 60 Major Amendments up to Protocol Version [redacted] (dated [redacted], 20[redacted]) of Study COV005

	Description of change (Protocol Version No.)	Reason for change
Dosage regimen	(1) The dose interval was changed from 28 ± 3 days to 28 ± 7 days (Version [redacted], [redacted], 20[redacted]). (2) Changed to 2-dose schedule (Version [redacted], [redacted], 20[redacted]) (3) Clarification of the timing of the second dose in participants who have developed COVID-19 or asymptomatic SARS-CoV-2 infection before the second dose (Version [redacted], [redacted], 20[redacted])	(1) To align with the design of UK Study COV001. (2) In response to the safety and immunogenicity results from Study COV001, the Data Safety Monitoring Board in charge of Studies COV001 to COV005 recommended the 2-dose regimen in this study. (3) To ensure that the second dose is administered only if the participant is clinically stable and has sufficiently recovered from COVID-19.
Sample size	(1) The number of participants in Group 2 was increased by 2150: from 550 to 2700 participants (2800 in total). (Version [redacted], [redacted], 20[redacted]) (2) The total number of participants was decreased from 2800 to 2000 (Group 2a, from 550 to 250; Group 2b, from 2150 to 1650) (Version [redacted], [redacted], 20[redacted]) (3) The number of participants in Group 1 was increased from 50 to 70, with a resulting increase in the total number of participants from 2000 to 2020 (Version [redacted], [redacted], 20[redacted]). (4) The number of participants in Group 3 was increased from 50 to 100, with a resulting increase in the total number of participants to 2070 (Version [redacted], [redacted], 20[redacted]).	(1) The sample size was increased because the spread of SARS-CoV-2 infection is unpredictable and the incidence of COVID-19 in Study COV001 was lower than expected. (2) The sample size was re-calculated based on the incidence in the placebo group as 2.5% to 3.5%. (3) To ensure an adequate number of evaluable patients in the safety cohort. Six of the first 24 participants tested positive for SARS-CoV-2 by nasal swab at enrollment; this proportion of non-evaluable participants was higher than expected. (4) Since approximately 1/3 are expected to be seropositive for SARS-CoV-2, approximately 30 seronegative participants can be secured with a sample size of 100 participants.
Inclusion criteria	The upper age limit of participants was elevated from ≤55 to ≤65 years old (Version [redacted], [redacted], 20[redacted])	This change was made according to the following recommendation of the Clinical Ethics Committee: Although the prevalence of comorbidities increases with increasing age, all adults ≥55 years old are not vulnerable and should be offered an opportunity to participate in this study if they meet the inclusion criteria and none of the exclusion criteria.
Exclusion criteria	(1) Added: Individuals with prior or current COVID-19 (Version [redacted], [redacted], 20[redacted]). (2) Deleted: COVID-19 serological testing at the screening visit to exclude individuals with prior SARS-CoV-2 infection (Version [redacted], [redacted], 20[redacted])	(1) Participants with current or prior SARS-CoV-2 infection are excluded to avoid heterogeneity in population and impact on immunogenicity assessment. (2) The FDA guidelines recommend no screening for prior SARS-CoV-2 infection. Further, the benefit/risk in the population with prior SARS-CoV-2 infection should be assessed. In addition, timely provision of serology results was difficult due to distribution issues at the laboratory.
Primary endpoints	The primary efficacy endpoint was defined as "COVID-19 that occurred ≥15 days after the second dose" (Version [redacted], [redacted], 20[redacted]).	This change was made because the 2-dose schedule was adopted based on data from Study COV001 that showed an improvement of immunogenicity.

11.4 Adverse Events of Special Interest

In Japanese Study D8111C00002 and foreign Studies COV001, COV002, COV003 and COV005, adverse events of special interest (AESI) have been established as shown in Table 61, based on the Brighton Collaboration case definition (Safety Platform for Emergency vACcines [SPEAC] project, 2020, https://media.tghn.org/articles/COVID-19_AESIs_SPEAC_V1.1_5 Mar2020.pdf [last accessed: April 6, 2021]), clinical experience, and scientific interest.

Table 61 Adverse Events of Special Interest

Body System	Medical Concept
Neurologic	Generalized convulsion: Seizures are episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. These may also manifest as sensory disturbances, autonomic dysfunction and behavioral abnormalities, and impairment or loss of consciousness.
	Guillain-Barre syndrome: Guillain-Barre syndrome is a peripheral demyelinating disease that may manifest as a temporary ascending paralysis.
	Acute disseminated encephalomyelitis (ADEM): ADEM is defined as a monophasic syndrome of inflammation and demyelination of the brain that occurs temporarily in association with infection or existing immunological inoculation, such as vaccination. ADEM most commonly occurs in the pediatric population.
	Other neurologic events: Newly occurring (acute or subacute) motor and sensory disturbances (e.g., weakness, numbness, paresthesia, hypoesthesia, hyperesthesia, dysesthesia), bowel/bladder dysfunction, gait impairment, visual disturbance, or events of myelitis, encephalomyelitis, transverse myelitis, or other sudden neurological disorder.
Vascular	Thrombotic, thromboembolic, and neurovascular events: Events that can manifest as transient or permanent vision disorders, dizziness, trouble understanding, facial paralysis, slurred speech, unilateral weakness, deep vein thrombosis with swollen, warm or painful leg, or pulmonary embolism with shortness of breath, chest pain or arrhythmia
Hematologic	Thrombocytopenia: A disorder causing an abnormal decrease in platelet count. A normal platelet count ranges from 150000 to 450000 platelets/μL
Immunological	Vasculitides: A group of related disorders characterized by inflammation of blood vessels (vasculitis) leading to tissue or end-organ damage
	Anaphylaxis: An acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction requiring immediate medical attention.
	Vaccine-associated enhanced respiratory disease (VAERD): The pathogenesis of VAERD is linked to a vaccine immune response characterized by induction of non-neutralizing antibodies, and a T-cell response of the Th2 type with hypereosinophilia (*Vaccine.* 2020; 38:4783-91). VAERD may manifest as a severe form of respiratory disease with prolonged pyrexia, and diverse clinical manifestations of disease severity and pathological changes characterized by increased areas of lung consolidation, broncho-interstitial pneumonia, and necrotizing bronchitis (*J Gen Virol.* 2016; 97:1489-99).
	Potential immune-mediated conditions: A group of autoimmune inflammatory disorders characterized by an alteration in cellular homeostasis,[a)] which may or may not have an autoimmune etiology.

a) Gastrointestinal disorders (Celiac disease, Crohn's disease, colitis ulcerative, proctitis ulcerative), liver disorders (autoimmune cholangitis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis), metabolic disorders (Addison's disease, autoimmune thyroiditis [including Hashimoto' thyroiditis], type 1 diabetes mellitus, Grave's or Basedow's disease), musculoskeletal disorders (antisynthetase syndrome, dermatomyositis, juvenile chronic arthritis [including Still's disease], mixed connective tissue disorder, polymyalgia rheumatica, polymyositis, psoriatic arthropathy, relapsing polychondritis, rheumatoid arthritis, scleroderma including diffuse systemic and CREST syndrome, ankylosing spondylitis, reactive arthritis [Reiter's syndrome], spondyloarthritis including undifferentiated spondyloarthritis, systemic lupus erythematosus, and systemic sclerosis), neuroinflammatory disorders (acute disseminated encephalomyelitis including site specific variants [e.g., non-infectious encephalitis, encephalomyelitis, myelitis, neurological meningitis], cranial nerve disorders including paralysis/paresis [e.g. Bell's palsy], Guillain-Barre syndrome including Miller Fisher syndrome and other variants, immune-mediated peripheral neuropathies and plexopathy including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy, multiple sclerosis, neuromyelitis optica spectrum disorder, narcolepsy, optic neuritis, transverse myelitis, myasthenia gravis including Eaton-Lambert syndrome), skin disorders (alopecia areata, autoimmune bullous skin disorders including pemphigus, pemphigoid, dermatitis herpetiformis, cutaneous lupus erythematosus, erythema nodosum, morphoea, lichen planus, psoriasis, rosacea, Sweet's syndrome, vitiligo), vasculitides (large vessels vasculitis including giant cell arteritis such as Takayasu's arteritis and temporal arteritis, medium sized and/or small vessels vasculitis including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome [allergic granulomatous angiitis], Buerger's disease, thromboangiitis obliterans, necrotizing vasculitis, and anti-neutrophil cytoplasmic antibody positive vasculitis [type unspecified], Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis), others (antiphospholipid syndrome, autoimmune hemolytic anaemia, autoimmune glomerulonephritis [including IgA nephropathy, rapidly progressive glomerulonephritis, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis], autoimmune myocarditis/cardiomyopathy, autoimmune thrombocytopenia, Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anaemia, Raynaud's phenomenon, sarcoidosis, Sjogren's syndrome, Stevens-Johnson syndrome, and uveitis

11.5 Background of the Use of Vaxzevria at a Dose Lower Than the Planned Dose Due to an Error in the Quantitative Value of Viral Load in Studies COV002 and COV005 (CTD 5.3.5.4.1)

During the conduct of Study COV002, [redacted] (a contract manufacturer of the study vaccine) and [redacted] of the University of Oxford were found to be using different methods to quantify viral particles (spectrophotometry or qPCR), resulting in approximately a 2.3-fold difference in determined vp. In consultation with MHRA, it was

agreed to use the dose based on viral particle content determined by spectrophotometry in Study COV002, to maintain consistency with Study COV001 and prevent participants from receiving a higher dose than planned. This resulted in selection of a dose of 5×10^{10} vp by spectrophotometry (2.2×10^{10} vp by qPCR). However, participants receiving this dose experienced adverse reactions less frequently than those in Study COV001, and further investigations identified an unexpected interference of an excipient, Polysorbate 80, with spectrophotometry. Although the cause is unknown, the content of Polysorbate 80 was approximately 2-fold in some batches of the study vaccine manufactured by [redacted] (Batch [redacted], [redacted], and [redacted]). As Polysorbate 80 amplifies the absorbance, it led to overestimation of the viral particle concentration. This overestimation led to over-dilution of the vaccine product concentration in the vial, resulting in administration of 45% of the intended dose to some participants (some participants in Group 1, 2, 4, and 5) in Study COV002. Polysorbate 80 is used as an excipient to prevent aggregation of adenoviral particles and stabilize them. The high concentration of Polysorbate 80 in the vaccine product of the batches does not affect the product quality or stability. Subsequently, with the permission of MHRA and DSMB, a decision was made to use the qPCR-determined 5×10^{10} vp dose as SD dose thereafter because of the higher assay precision of qPCR.

In Study COV005, the viral particle content in the vaccine product measured with qPCR by [redacted] was overestimated, and some of the initial participants (in Groups 2a and 2b) were given a dose lower than the standard dose. This issue was identified in a retrospective measurement performed by the applicant (AstraZeneca). The vp content in the vaccine product was remeasured by commercially optimized qPCR and digital droplet PCR (dd PCR); the results showed that the qPCR data on [redacted] product batch [redacted] were overestimated than the actual values. Following consultation with the South African regulatory authority, the dose level was adjusted based on the values obtained by the remeasurement, to achieve a dose comparable to SD used in the other studies.

Accordingly, in the pooled analyses, the doses of Vaxzevria (SD or LD) were classified according to the following criteria (see Section 11.1):

- SD is defined as 5×10^{10} vp measured by spectrophotometry or qPCR. This includes vaccine products with a range of ± 30% (3.5 to 6.5×10^{10} vp).
- LD is defined as 2 to 2.5×10^{10} vp measured by qPCR.

As described above, the analysis population in the pooled analyses includes participants who received doses measured by different quantitation methods in a single vaccination group (LD or SD). The applicant provided the following explanation:

> The vaccine products used in clinical studies were manufactured by 3 different manufacturing processes at 3 different manufacturing sites, but they were shown to be comparable to each other, with no meaningful differences in viral particle concentration at SD or infectivity titer per VP (see Section 2.R.2). Therefore, the change in analytical procedure of the vaccine products have no impact on the evaluation of clinical study data of Vaxzevria.

Report on Special Approval for Emergency (2)

May 13, 2021

Product Submitted for Approval

Brand Name	Vaxzevria Intramuscular Injection
Non-proprietary Name	COVID-19 (SARS-CoV-2) Vaccine (Recombinant Chimpanzee Adenovirus Vector)
Applicant	AstraZeneca K.K.
Date of Application	February 5, 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 view presented in Section "7.R.1 Clinical Data Package and Review Policy" of Report (1) was supported by the expert advisors.

1.2 Efficacy

In the expert discussion, the expert advisors supported PMDA's view presented in Section "7.R.2 Efficacy" of Report (1), while giving the following comments:

- PMDA focused on whether the efficacy of Vaxzevria can be evaluated taking into consideration of the impact of dose intervals, rather than whether an optimal dose interval can be evaluated, on the assumption that dose intervals will have an impact. The expert advisors support this policy on reviewing the efficacy.
- The possibility of very low vaccine efficacy of Vaxzevria against the B.1.351 strain should be communicated appropriately to healthcare professionals.

PMDA communicated the above opinions of the expert advisors to the applicant, and the applicant responded that they would take appropriate actions.

1.3 Safety

1.3.1 Trends in Europe, etc. after Report (1) and PMDA's View

As the additional information to Section "7.R.3.2.3 Thrombotic, thromboembolic, and neurovascular events" of Report (1), the trends in European and other countries and PMDA's view (as of April 9, 2021) after preparation of Report (1) are described below. At the expert discussion, the expert advisors gave their comments on PMDA's view as described in Section 1.3.2 [2].

PMDA confirmed the trends of actions taken by European authorities, etc. for thrombotic, thromboembolic, and neurovascular events reported in foreign post-marketing settings. The details are described below.

On April 7, 2021, EMA announced that thrombosis with platelets decreased may occur very rarely after vaccination with Vaxzevria and the event should be listed as an adverse reaction to Vaxzevria (https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood [last accessed on May 11, 2021]). However, EMA stated that the reported combination of thrombosis and platelets decreased is very rare and the overall benefits of the vaccine in preventing COVID-19 outweigh the risks of adverse reactions. At that time, the majority of cases were reported in women aged <60 years and these events occurred within 2 weeks after the first dose of Vaxzevria, but with no identified risk factors. These assessments are based on a review of 62 cases of CVST and 24 cases of visceral venous thrombosis (including portal vein thrombosis and splenic vein thrombosis) reported in the European adverse reaction reporting database (EudraVigilance) by March 22, 2021, at which time approximately 25 million people had been vaccinated with Vaxzevria in the EEA and UK. As a possible mechanism of development of thrombosis associated with platelets decreased, EMA stated that a condition similar to heparin-induced Thrombocytopenia (HIT), which is observed in patients receiving heparin, may be induced by immune response after vaccination.

On April 7, 2021, MHRA announced that although the benefits of vaccination still outweigh any risks, evidence suggested the relationship between Vaxzevria and very rare cases of specific thrombosis with platelets decreased (https://www.gov.uk/government/news/mhra-issues-new-advice-concluding-a-possible-link-between-covid-19-vaccine-astrazeneca-and-extremely-rare-unlikely-to-occur-blood-clots [last accessed on May 11, 2021]). By March 31, 2021, 79 cases of thrombosis with platelets decreased following vaccination with Vaxzevria have been reported in UK. Details are as follows:

- Of the 79 cases, 44 were CVST with thrombocytopenia and the remaining 35 were thrombosis in other major vessels with thrombocytopenia.
- These cases occurred in 28 men and 51 women aged 18 to 79 years (at that time, more women had been vaccinated with Vaxzevria than men).
- In total, 19 people (6 men and 13 women) died; 11 of the 19 people were aged <50 years, including 3 people aged <30 years. Of the 19 cases leading to death, 14 were CVST with thrombocytopenia and 5 were thrombosis with thrombocytopenia.
- All 79 cases occurred after the first dose.

MHRA did not recommended any age restriction for recipients of Vaxzevria, but the statement by the Joint Committee on Vaccination and Immunisation (JCVI), which was issued at the same time, describes that it is desirable for healthy adults aged <30 years to receive an alternative COVID-19 vaccine, considering the balance between benefits (prevention of ICU admission due to COVID-19) and potential risks of Vaxzevria (https://www.gov.uk/government/publications/use-of-the-astrazeneca-covid-19-vaccine-jcvi-statement [last accessed on May 11, 2021]) [29)].

As of April 9, 2021, WHO and some countries recommend vaccination with Vaxzevria without any particular restriction. In some countries, however, vaccination with Vaxzevria are restricted only to people aged ≥30 years, ≥50 years, ≥55 years, ≥60 years, ≥65 years, or ≥70 years, and other countries have announced suspension of vaccination with this vaccine.

PMDA's view:
After the market launch, multiple thrombotic events occurred within 2 weeks after vaccination with Vaxzevria in multiple foreign countries, and some of them resulted in serious outcome and led to death. Taking into account this fact and the foreign trends, etc., the package insert should call attention to "thrombosis" as a major adverse reaction. The reported cases include serious thrombosis without thrombocytopenia and deaths, and the mechanism of development of thrombosis following vaccination with Vaxzevria remains to be elucidated. Therefore, the package insert should call attention to "thrombosis," not limiting to "thrombosis with thrombocytopenia."

Very rare events such as CVST are included in the cases of thromboses with thrombocytopenia reported in foreign post-marketing settings, and many of them have been reported in non-elderly people. In addition, undesirable treatment procedures such as the use of heparins have become clear. Taking these findings into account, the applicant should use the package insert or materials to disseminate information including the following: thrombosis reported after vaccination with Vaxzevria, the details of the cases of thrombosis (e.g., site of onset, outcome), time to onset (mostly within 2 weeks after vaccination with Vaxzevria), symptoms of concerns, and information on diagnosis and treatment.

At present, there are biases in the baseline characteristics of recipients of Vaxzevria (e.g., gender, age) in the foreign post-marketing settings. No risks factors such as gender, detailed age group, and medical history have been identified for thromboses observed after vaccination with Vaxzevria. The risks of being affected by COVID-19 may differ depending on the pandemic situation of SARS-CoV-2, age, and other factors. Taking these matters into account, it is considered difficult to make judgments on routine risks by gender and age. On the other hand, clinical studies have demonstrated the efficacy of Vaxzevria in adults in a wide range of age groups. Therefore, it is not appropriate to set restrictions on genders and age groups for the approval of Vaxzevria, considering the balance between benefits and the above risks of SARS-CoV-2 vaccines. The target populations

29) On May 7, 2021, the statement by the JCVI in the UK was modified to recommend that healthy adults aged <40 years receive alternative vaccines, in response to situations such as the status of SARS-CoV-2 infection and the availability of vaccines other than Vaxzevria (https://www.gov.uk/government/publications/use-of-the-astrazeneca-covid-19-vaccine-jcvi-statement-7-may-2021/use-of-the-astrazeneca-covid-19-azd1222-vaccine-updated-jcvi-statement-7-may-2021 [last confirmation date:: May 11, 2021]).

for vaccination with Vaxzevria should be determined flexibly according to the pandemic status of SARS-CoV-2 and the availability of alternatives such as vaccines other than Vaxzevria. The target population for the public vaccination program of SARS-CoV-2 vaccines can be determined based on the "Vaccination Implementation Regulations," "Provisional Implementation Guidelines for Vaccinations Against COVID-19," etc.; this makes it possible to discuss and determine the appropriate target populations for Vaxzevria in Japan. There have been no changes in the scope of approval (or use authorization) of Vaxzevria in countries that introduced age restrictions for recipients of Vaxzevria or suspended vaccination with Vaxzevria.

In the applicant-proposed surveillance, pharmacovigilance activities, etc. to be conducted after the market launch of Vaxzevria, the applicant should examine matters such as the incidence of thrombotic events after vaccination with Vaxzevria in Japan, risk factors for such events, and characteristics of people who should not be vaccinated with Vaxzevria. If any thrombotic events suspected to be related to Vaxzevria are reported in the pharmacovigilance activities for Vaxzevria in post-marketing settings, the applicant should collect information that enables assessment of risks factors, etc. for the events (patient characteristics, concomitant drugs, medical history, laboratory data, etc.) and examine the necessity of new precautions. To this end, the applicant should also consider collaboration with related academic societies and medical institutions and establish a system for information collection and evaluation. It is important to examine thrombotic events in the general use-results survey and the specified use-results survey which are currently being planned by the applicant, but new findings are unlikely to be found by these surveys because of the low incidence of the events. Therefore, the applicant should also consider conducting observational studies using existing databases, etc. and the feasibility of such studies.

1.3.2 Discussion on Safety at the Expert Discussion

[1] Safety profile

In the expert discussion, the expert advisors supported PMDA's view presented in Section "7.R.3.1 Safety profile" of Report (1) while giving the following comments:

- There is no particular concern because many of solicited adverse events and unsolicited adverse events occur immediately after vaccination, with few serious adverse events reported, However, information on the long-term safety is limited, and therefore appropriate risk assessment is necessary.
- The collection and evaluation of Japanese and foreign information should be continued, but this does not preclude approval of Vaxzevria.

[2] Adverse events and adverse reactions of special interest

In the expert discussion, the expert advisors supported PMDA's views presented in Section 1.3.1 above and Section "7.R.3.2 Adverse events and adverse reactions of special interest" of Report (1), while giving the following comments:

- Thrombosis with thrombocytopenia has been reported to occur very rarely following vaccination with Vaxzevria. Some reports revealed that thrombosis with thrombocytopenia occurring after vaccination with Vaxzevria is pathologically similar to HIT, which is observed in patients on heparins therapy. There is also a report that antibodies against platelet factor 4 (PF4), which are detected as HIT antibodies, were found in

many patients (*N Engl J Med.* 2021; DOI: 10.1056/NEJMoa2104840, *N Engl J Med.* 2021; 10.1056/NEJMoa2104882, *N Engl J Med.* 2021; 10.1056/NEJMoa2105385).

- Subsequent surveys on thrombotic events reported in European and other countries have revealed their symptoms and undesirable treatments (e.g., the use of heparins) for the events. If guidelines for diagnosis and treatment of such events are developed, shared among healthcare professionals, and thoroughly disseminated in clinical practice, appropriate diagnosis and treatment can save patients who may die due to thrombotic events occurring after vaccination with Vaxzevria.
- The risk of thrombosis after vaccination with Vaxzevria is extremely low. Exacerbation of thrombosis can be prevented by providing appropriate treatment when symptoms such as abdominal pain occur.
- Since CVT/CVST and visceral venous thrombosis, which are very rarely encountered in clinical practice, have been reported, adequate information and advice should be provided to relevant healthcare professionals such as physicians specializing in stroke who provide medical care for CVT, physicians specializing in medical care for headache, gastroenterologists and gastrointestinal surgeons who provide medical care for abdominal pain as an initial symptom of visceral venous thrombosis.
- Heparin therapy usually performed for venous thrombosis is likely to aggravate thrombosis occurring after vaccination with Vaxzevria. High-dose immunoglobulin therapy is used for the treatment of thrombosis occurring after vaccination with Vaxzevria in European and other countries, but in Japan its use for thrombosis is off-label. In addition, appropriate HIT antibody tests results may be obtained only by off-label use of ELISA. (According to a literature report, patients who experienced thrombosis after vaccination with Ad26.COV2.S [an adenovirus vector vaccine intended to prevent COVID-19 as with Vaxzevria] tested negative for HIT antibodies with latex turbidimetric immunoassay [labeled use in Japan], but tested positive with ELISA [off-label in Japan]. [*N Engl J Med.* 2021; DOI: 10.1056/NEJMc2105869]).
- Collaboration with related academic societies and medical institutions is essential in preventing aggravation of thrombosis occurring after vaccination with Vaxzevria and collecting and evaluating information on the event, and therefore the collaborative system should be established among the related organizations.
- The comprehensive term “thrombosis” listed in the “significant adverse reactions” section may resulting in a delay in the suspicion of thrombosis/thromboembolism in each organ. In contrast, if “thrombosis with thrombocytopenia” is listed in the section, it may trigger the suspicion of an event that causes thrombocytopenia, leading to the diagnosis of such event in some cases.
- Thrombosis after vaccination with Vaxzevria may occur even in young people who are generally considered to be at the low risk of severe COVID-19, and may become severe once it occurs. Therefore, a certain age restriction is inevitable if Vaxzevria is approved in Japan.
- No risk factors for thrombosis after vaccination with Vaxzevria have been identified at present. Therefore, the expert advisors understand PMDA’s views that no special restrictions should be placed on the approval of Vaxzevria, and that appropriate target populations for vaccination with Vaxzevria can be discussed and determined in the public vaccination program after the approval of Vaxzevria.
- Thrombotic events after vaccination with Vaxzevria are considered to be very rare events that occur basically in about 1 in 100,000 people, and therefore it is difficult to call attention to the events based on the results of a prospective study in Japanese people. The applicant should consider using foreign databases proactively, in addition to using existing databases in Japan, for the collection and evaluation of post-

marketing data.

PMDA provided the following explanation about the provision of information on thrombotic events after vaccination with Vaxzevria to healthcare professionals and the development of diagnosis and treatment guidelines:
Some academic societies have already said that they are willing to assist the development of diagnosis and treatment guidelines. PMDA would like to make efforts for extensive information sharing and smooth operation of these guidelines without delay in cooperation with the MHLW and the applicant.

PMDA's view was supported by the expert advisors.

The expert advisors discussed PMDA's view that "thrombosis" is appropriate rather than "thrombosis with thrombocytopenia" as the term of the clinically significant adverse reaction. The expert advisors commented that a certain number of thromboses may occur irrespective of vaccination with Vaxzevria and all thromboses occurring after vaccination with Vaxzevria may be considered to be related to Vaxzevria if cautionary advice is provided for "thrombosis."

PMDA explanation:
"Thrombosis with thrombocytopenia" will be classified as an important identified risk and "thrombosis" as an important potential risk in the Risk Management Plan. The package insert will list "thrombosis" as a significant adverse reaction and state that serious thrombosis with thrombocytopenia, including very rare types of thrombosis such as CVST, have been observed after vaccination with Vaxzevria.

PMDA's view was finally supported by the expert advisors.

PMDA provided the following explanation about its conclusion that no restriction (e.g., gender and age) should be imposed on the approval of Vaxzevria:
For the practical use of Vaxzevria, more appropriate target populations for vaccination are likely to be set in the public vaccine vaccination program, taking into account matters such as the pandemic status of SARS-CoV-2 at that time point. The details of the present review may be also taken into consideration; therefore, PMDA would like to appropriately share comments made by the expert advisers at the expert discussion and utilize the comments for the practical use.

PMDA's view was finally supported by the expert advisors.

PMDA's explanation about the post-marketing surveys:
According to the applicant, it is difficult to appropriately conduct surveys using databases in Japan because (1) basically, vaccinations will not be recorded on claims data, (2) only a limited number of vaccination cases (information on vaccine recipients) will be recorded in electronic medical records of medical institutions, and (3) databases with a sample size of 1 million people are required to compare "cases of symptomatic COVID-19

and fatal cases" with "cases of thrombotic events and cases of fatal outcome after vaccination with Vaxzevria." In addition, PMDA also separately considered the feasibility of a database survey but it is difficult to investigate and analyze these events using a large-scale database in Japan, because (1) information on vaccination is currently possessed by individual local governments and therefore cannot be linked with medical information stored in existing databases, and (2) different medical institutions have different systems of electronic medical records, and not all of the systems can record information on vaccination.

In response to PMDA's explanation, the expert advisors gave the following comments:

- The national government should take the initiative for the implementation of surveys, etc. using a large-scale database.
- Academic societies, etc. have long pointed out the importance of linking information on vaccination for infection prevention and information on adverse events.
- Not only the Ministry of Health, Labour and Welfare but also relevant ministries and agencies should be involved in linking personal health information with other data.

PMDA provided the following explanation:
A system for the collection, evaluation, and feedback of adverse reaction information (including patient characteristics and laboratory data) in post-marketing settings will be appropriately established in Japan in cooperation with academic societies. It is possible to grasp the parameters of vaccine recipients for Vaxzevria in the public vaccination program, and therefore it is possible to grasp the incidence of these events by ensuring the collection of information in post-marketing settings. PMDA would like to continuously assess the risks of these events including the results of database surveys obtained from overseas.

PMDA's view was finally supported by the expert advisors.

PMDA communicated the above comments of the expert advisors to the applicant. The applicant responded that they would appropriately deal with the collection and evaluation of post-marketing safety information as well as the provision of information to healthcare professionals, vaccine recipients, etc.

The applicant's explanation about the historical incidence rate of thrombotic events in Japan:
Using the [redacted] database owned by [redacted], the incidence rate of thrombosis with thrombocytopenia (per 100,000 person-years) from December 2014 to November 2021 was calculated for each year by age group. The participants to be analyzed were those who were confirmed to be enrolled for at least 1 year starting in December every year and were able to be followed up for 1 year after the starting point. In the analysis years (5 years in total), the incidence rate of thrombosis with thrombocytopenia in Japan by age group was as follows:

- 0.402-1.391 per 100,000 person-years for the age of 10-19 years
- 0.223-0.713 per 100,000 person-years for the age of 20-29 years
- 0.526-1.205 per 100,000 person-years for the age of 30-39 years
- 0.383-2.468 per 100,000 person-years for the age of 40-49 years
- 1.540-3.101 per 100,000 person-years for the age of 50-59 years

- 3.121-9.326 per 100,000 person-years for the age of 60-69 years
- 2.574-18.755 per 100,000 person-years for the age of 70-74 years

In the same analysis years (5 years in total), the incidence rate of CVST (regardless of thrombocytopenia) in Japan by age group was as follows:

- 0.000-0.418 per 100,000 person-years for the age of 10-19 years
- 0.180-0.890 per 100,000 person-years for the age of 20-29 years
- 0.351-0.904 per 100,000 person-years for the age of 30-39 years
- 0.785-1.208 per 100,000 person-years for the age of 40-49 years
- 0.264-1.820 per 100,000 person-years for the age of 50-59 years
- 0.602-2.808 per 100,000 person-years for the age of 60-69 years
- 0.000-12.502 per 100,000 person-years for the age of 70-74 years

The detailed plans for post-marketing surveys, etc. are discussed in Section 1.7.

1.4 Clinical Positioning and Vaccination in Special Populations

In the expert discussion, the expert advisors supported PMDA's views presented in Sections "7.R.3.3 Safety in special populations" and "7.R.4 Clinical positioning and vaccination in special populations" of Report (1), while giving the following comments:

- The SARS-CoV-2 vaccine currently available in Japan has limitations in distribution, shipping, and storage; and this causes bottlenecks in establishing a management system of the vaccine in some regions. Vaxzevria can be stored in a refrigerator at 2°C to 8°C and will lead to faster and broader vaccination.
- Women in late pregnancy or immediately after childbirth are at high risk of CVT, and therefore alternative vaccines should be recommended rather than Vaxzevria, which may cause thrombosis, if other vaccines with no reports of thrombosis are available. Other recommendations, such as advising pregnant women to avoid vaccination during 1 month before delivery, may also be acceptable.

PMDA's explanation about vaccination in pregnant women:
At present, there is no evidence regarding vaccination with Vaxzevria in pregnant women and the risk of thrombosis is generally high in this population, but whether Vaxzevria will further increase the risks is unknown. It is difficult to make a precautionary statement for pregnant women during the review, and vaccination in pregnant women in clinical practice will be appropriately handled in the public vaccination program, as with the case of ages and dose interval.

PMDA's view was finally supported by the expert advisors.

1.5 Indication

PMDA's view presented in Section "7.R.5 Indication" in Report (1) was supported by the expert advisors.

1.6 Dosage and Administration

In the expert discussion, the expert advisors supported PMDA's view presented in Section "7.R.6 Dosage and administration" of Report (1) while giving the following comments:

- The expert advisors agree with PMDA's view, but the dose interval to be used for Vaxzevria in the post-marketing clinical practice should be discussed and determined in the future.
- Although determining the appropriate dose interval is difficult, a longer dose interval is beneficial for widespread vaccination for people in Japan, because the supply of SARS-CoV-2 vaccines is uncertain in Japan.

PMDA's explanation:
For the practical use of Vaxzevria, more appropriate dose interval and target populations for vaccination are likely to be defined in the public vaccine vaccination program, taking into account matters such as the pandemic status of SARS-CoV-2 at that time point. The details of the present review may be also taken into consideration; therefore, PMDA would like to appropriately share the comments made by the expert advisers at the expert discussion and utilize the comments for the practical use.

PMDA's view was supported by the expert advisors.

Based on the above discussion, PMDA asked the applicant to provide the following cautionary advice in the "Precautions Concerning Dosage and Administration" section, and the applicant responded that they would take appropriate actions.

Precautions Concerning Dosage and Administration
Vaxzevria should be administered to people ≥18 years old.
To achieve the maximum effect of Vaxzevria, it is desirable to administer Vaxzevria at an interval of >8 weeks.

1.7 Post-marketing investigations

In the expert discussion, the expert advisors supported PMDA's view presented in Section "7.R.7 Post-marketing investigations" of Report (1).

PMDA asked the applicant to explain the collection, evaluation, and provision of post-marketing information on thrombosis, taking into account the current status.

The applicant's explanation:
The applicant plans to collect information on adverse reactions and detailed information using separate questionnaires for each event, and to gather information through the general use-results survey (long-term follow-up) and specified use-results survey (individuals with underlying disease who are at high risk of severe COVID-19), and by other means. The collected information will be promptly evaluated, and the necessity of further safety assurance measures will be discussed by referring to the historical incidence rate in Japan which was preliminarily investigated (see Section 1.3.2 [2]). In addition, the applicant will establish an external expert panel in Japan to appropriately provide information to healthcare professionals and vaccine recipients based on

the advice of external experts, as necessary, when thrombosis with thrombocytopenia is reported. In US and EU/UK, an observational study with a 2-year observation period is planned to investigate the safety specification, the incidence and relative risks of adverse events of special interest after vaccination with Vaxzevria using databases. In addition, in US, EU, and UK, a prospective cohort study will be conducted to investigate the incidence of serious adverse events, adverse events of special interest, etc. in a total of 30,000 people for 3 months after vaccination. Furthermore, nonclinical studies and *in vitro* studies will be conducted to elucidate the mechanism of onset of thrombosis with thrombocytopenia.

To communicate information to healthcare professionals, the applicant plans to disseminate information promptly through the website for healthcare professionals. Materials such as the latest proper use guide will be posted on the website for healthcare professionals to disseminate information on the incidence of thrombosis with thrombocytopenia in foreign post-marketing settings, guidelines for diagnosis and treatment, and appropriate provision of information to vaccine recipients. This website will provide the latest safety information if thrombosis with thrombocytopenia is reported after the start of vaccination in Japan. Guidelines for diagnosis and treatment will be developed based on foreign guidelines and advice from external experts in Japan and provided to healthcare professionals as Japanese practical guidelines.

The applicant plans to disseminate information to vaccine recipients via the website for vaccine recipients. The latest materials for vaccine recipients will be posted on the website, to let them know the following: (a) The fact that thrombosis with thrombocytopenia has been reported after vaccination with Vaxzevria in foreign countries; (b) the types and timing of onset of related symptoms; (c) and the need to make an emergency visit to a medical institution at the onset of any symptom. A two-dimensional code of the link to the website for vaccine recipients will be shown on the vaccination sticker to be attached to the certificate of vaccination, and printed materials for vaccine recipients will be provided to facilities based on the number of vials at the time of delivery of Vaxzevria.

In view of the discussion above, PMDA concluded that the current Risk Management Plan (draft) for Vaxzevria should include the safety specification presented in Table 62, and that the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Tables 63 to 65.

Table 62 Safety and Efficacy Specifications in the Risk management Plan (draft)

Safety specification		
Important identified risks [a)]	Important potential risks [b)]	Important missing information [c)]
・Shock, anaphylaxis ・Thrombosis with thrombocytopenia	・Immune-mediated neurological reactions ・Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) ・Thrombosis	・Safety in individuals with underlying diseases who are at high risk of severe COVID-19 ・Safety of vaccination in pregnant or lactating women
Efficacy specification		
Not applicable		

a) Significant adverse events whose relationship with the drug (vaccine) has been demonstrated based on sufficient evidence.
b) Significant adverse events for which there are factors suspected to be related to the drug (vaccine) but there is not sufficient evidence from clinical data, etc.
c) Significant information that is insufficient to predict the post-marketing safety of the drug (vaccine) because adequate information was not obtained at the time when the Risk Management Plan was formulated.

Table 63 Summary of Additional Pharmacovigilance Activities and Risk Minimization Activities in the Risk Management Plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
・Early post-marketing phase vigilance ・General use-results survey (long-term follow-up) ・Specified use-results survey (individuals with underlying diseases who are at high risk of severe COVID-19) ・Post-marketing clinical study [Japanese Study D8111C00002] ・Studies COV001, COV002, COV003, and COV005 included in foreign pooled analysis ・US Study D8110C00001	・Disseminate data gathered through early post-marketing phase vigilance ・Prepare and provide materials for healthcare professionals (proper use guide) ・Prepare and provide materials for the general public (for people who receive Vaxzevria Intramuscular Injection and their families) ・Periodic publication of the incidence of adverse reactions

Table 64 Outline (draft) of the General Use-Results Survey Plan for Healthcare Professionals, etc.

Objective	To confirm long-term safety up to 12 months after the second dose of Vaxzevria (conducted as a follow-up investigation for the health status survey in priority vaccine recipients [a)])
Population	All individuals who consented to participate in the 12-month follow-up after participating in the health status survey in priority vaccine recipients
Observation period	From 1 month (the end of the observation period of the health status survey in priority vaccine recipients) to 12 months after the second dose
Planned sample size	All individuals who consented to participate in the 12-month follow-up after participating in the health status survey (planned number of participants: 10,000-20,000) in priority vaccine recipients
Main survey items	Baseline characteristics of vaccine recipients (e.g., medical history, complications, history of allergies, and pregnancy/lactation status [female only]), status of vaccination with Vaxzevria, information on vaccination with other vaccines, concomitant drugs, serious adverse events (including thrombosis with thrombocytopenia, immune-mediated neurological reactions, vaccine-associated enhanced disease [VAED] including vaccine-associated enhanced respiratory disease [VAERD], and thrombosis), COVID-19-related information (SARS-CoV-2 test information; presence or absence of COVID-19 symptoms, date of diagnosis, and treatment/procedure in individuals who tested positive for SARS-CoV-2), etc.

a) A survey to collect safety information between the first dose of Vaxzevria to 1 month after the second dose in healthcare professionals, caregivers, or healthy adults recruited for vaccination at facilities included in the survey. This survey is being planned by the study group for the research project funded by the Health Sciences Research Grant of the Ministry of Health, Labour and Welfare.

Table 65 Outline of the Specified Use-Results Survey (draft) in Individuals with Underlying Diseases Who Are at High Risk of Severe COVID-19

Objective	To confirm the safety in Vaxzevria recipients with underlying diseases who are at high risk of severe COVID-19
Survey method	Centralized registration method
Population	Vaxzevria recipients with underlying diseases who are at high risk of severe COVID-19 (including patients with severe or poorly controlled underlying diseases)
Observation period	From the day of the first dose to 28 days after the second dose
Planned sample size	1,000 vaccine recipients
Main survey items	Baseline characteristics of vaccine recipients (e.g., medical history, complications, history of allergies, and pregnancy/lactation status [female only]), status of vaccination with Vaxzevria, information on vaccination with other vaccines, concomitant drugs, adverse events (including shock/anaphylaxis, thrombosis with thrombocytopenia, immune-mediated neurological reactions, vaccine-associated enhanced disease [VAED] including vaccine-associated enhanced respiratory disease [VAERD], and thrombosis), COVID-19-related information (SARS-CoV-2 test information; presence or absence of COVID-19 symptoms, date of diagnosis, and treatment/procedure in individuals who tested positive for SARS-CoV-2), etc.

The general use-results survey is planned to be conducted in healthcare professionals, etc. and the specified use-results survey in individuals with underlying diseases who are at high risk of severe COVID-19. However, the target populations for vaccination with Vaxzevria may be changed depending on the progress of vaccination with the already-approved SARS-CoV-2 vaccine. PMDA therefore asked the applicant to reconsider the details of the survey plan as appropriate after confirming the target populations for vaccination with Vaxzevria at the start of survey. The applicant responded that they would take appropriate actions.

1.8 Quality

1.8.1 Addition of Manufacturing Site of Vaccine Product

As a result of technology transfer of Process D (see Table 5 in Section 2.2.3 in Report (1)), [redacted] was newly added as a manufacturing site of vaccine product. After the completion of Report (1), the applicant submitted the results of process validation and batch analysis of the vaccine product

manufactured by [redacted]. Based on the results, PMDA confirmed the comparability of quality attributes (description, pH, osmotic pressure, infectivity titer, identification, viral particle concentration, DNA:protein ratio, viral particle:infectious viral particle ratio, polysorbate 80 concentration, insoluble particulate matters, extractable volume, and bacterial endotoxins) between the vaccine product of [redacted] and that of [redacted] (both made by Process D). However, the applicant should submit the results of ongoing long-term testing performed at [redacted] to PMDA as soon as they are obtained.

1.8.2 Shelf Lives of Active Substances and Vaccine Products

The applicant submitted the results of the stability tests of active substance and vaccine product that were ongoing at the time of preparing Report (1), as shown below.

Table 66 Stability Tests of Active Substance (as of April 2021)

	Storage condition	Manufacturing process	Number of batches	Test period	Storage form
Long-term [1)]	-90°C to -55°C	Process (c) [3)]	1	7 months [5)]	[redacted] container
			1	6 months	
			1	5 months [6)]	
		Process (d) [4)]	6	2 months	[redacted] container
	5 ± 3°C[2)]	Process (c)	1	8 months	[redacted] container
			2	6 months	
		Process (d)	6	2 months	[redacted] container

1) Long-term tests (-90°C to -55°C and 5 ± 3°C) are ongoing and continued until 12 months.
2) This stability test is performed because [redacted].
3) Active substance of [redacted], 4) Active substance of [redacted]
5) Six months for description and pH; 6) Three months for description and pH

Table 67 Stability Tests of Vaccine Product (as of April 2021)

	Storage condition	Manufacturing process of active substance	Manufacturing process of vaccine product	Number of batches	Test period	Storage form
Long-term [1)]	5 ± 3°C, inverted	Process (c) [2)]	Process C [4)]	3	6 months [6)]	Glass vial, bromobutyl rubber stopper
		Process (d) [3)]	Process D [5)]	3	1.5 months	

1) The long-term tests are ongoing and continued for 12 months, 2) Active substance of [redacted], 3) Active substance of [redacted],
4) Vaccine product of [redacted], 5) Vaccine product of [redacted] or vaccine product of [redacted], 6) The data were submitted before the preparation of Report (1)

PMDA's view on the shelf lives of vaccine product and active substance:

In the long-term testing of active substance (-90°C to -55°C), no significant changes were identified until 7 months in the quality attributes (description, pH, infectivity titer, viral particle concentration, viral particle:infectious viral particle ratio) of active substance made by Process (c), and until 2 months in the quality attributes (description, pH, infectivity titer, viral particle concentration) of all 6 batches of active substance made by Process (d). In addition, the test results showed comparability between active substances made by Processes (c) and (d). Therefore, the shelf life of 6 months at -90°C to -55°C for active substance is acceptable.

In the long-term testing of vaccine product (5 ± 3°C), no significant changes were identified until 1.5 months in the quality attributes (infectivity titer, viral particle concentration, viral particle:infectious viral particle ratio, DNA:protein ratio) of vaccine product made by Process D. As described in Report (1), stability testing showed the stability until 6 months of major quality attributes (description, pH, infectivity titer, viral particle

concentration, viral particle:infectious viral particle ratio, container integrity, insoluble particulate matters, osmotic pressure) of 3 batches of vaccine product made by Process C. In addition, the test results showed comparability between vaccine products made by Processes C and D. Therefore, the shelf life of 6 months at 5 ± 3°C for vaccine product is acceptable.

However, the applicant should submit the results of the ongoing long-term testing (i.e., tests of 3 batches of active substance made by Process (d) and 3 batches of vaccine product made by Process D) to PMDA as soon as 6-month data are obtained.

1.8.3 Discussion on Tests for Adventitious Viruses, etc. in the Expert Discussion

In the expert discussion, the expert advisors presented the following comments on *in vitro* and *in vivo* tests for adventitious viruses etc. in the production culture process of active substance:

- There is no [redacted] process for Vaxzevria. Under ordinary circumstances, the applicant should consider performing tests for adventitious viruses, etc. on [redacted]. However, the applicant performed [redacted] because [redacted] required to [redacted] was limited. If tests for adventitious viruses, etc. are performed on [redacted], appropriate tests should be performed to confirm the absence of contamination with adventitious viruses in cell banks and virus seeds to be used for the production culture process.

PMDA explained the following points, and concluded that performing tests for adventitious viruses, etc. on [redacted] was acceptable. This conclusion was finally supported by the expert advisors.

- *In vitro* and *in vivo* tests for adventitious viruses etc. were performed on MCB, WCB, MVS, and WVS according to the test methods described in the European Pharmacopoeia (version 10.0). None of the tests identified contamination with adventitious viruses. PMDA considers these results ensure the viral safety of cell banks and virus seeds to be used for the production culture process.
- No contamination with adventitious viruses, etc. was identified by *in vitro* or *in vivo* tests for adventitious viruses, etc. performed on samples [redacted].

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

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

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

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

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

3.2 PMDA's conclusion concerning the results of 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 document submitted.

4. Overall Evaluation

As a result of the above review, 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

Two separate doses of 0.5 mL each should be administered intramuscularly at a 4- to 12-week interval.

Approval Conditions and Other Requirements

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item 1
   The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is limited information on the long-term stability, etc., at the current moment of the approval. Therefore, after the market launch, the applicant is required to continue to collect and report the information.
   (2) Matters related to Item 2
   When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.
   (3) Matters related to Item 3

The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to vaccine recipients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.

(4) Matters related to Item 4

The applicant is required to report the quantity of the product sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:

(1) The applicant is required to develop and appropriately implement a risk management plan.

(2) Since there is limited information on the product at the current moment, the applicant is required to promptly collect the safety data of the product, such as information on adverse reactions, after the market launch based on the pre-designed schedule, submit the data to the Pharmaceuticals and Medical Devices Agency (PMDA), and take necessary actions to ensure the proper use of the product. Information obtained from the national health survey, etc., should be reflected appropriately.

(3) Results of the ongoing or scheduled Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most updated information on the efficacy and safety of the product should be made easily accessible to healthcare professionals and vaccine recipients. The applicant is required to appropriately assist the government in disseminating information on the efficacy and safety of the product.

(4) The product is granted Special Approval for Emergency, in accordance with the provisions in Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. There is limited information on the long-term stability, etc., at the current moment of the approval. Therefore, after the market launch, the applicant is required to continue to collect and report the information.

(5) The efficacy and safety data of the product will be accumulated with the progress of the vaccination program. The applicant is required to appropriately instruct physicians to 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 who have provided written informed consent through the vaccine screening questionnaire in advance.

(6) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 6 months after the approval. If new data, etc., submitted in accordance with the approval conditions necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

3. The product is approved based on Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices

Act. The approval may be withdrawn in accordance with the provision in Article 75-3 of the Act in a case where (a) the product does not conform to one or more Items of Article 14-3, Paragraph 1 of the Act or (b) the withdrawal is necessary to prevent the emergence or expansion of public health risks.

Appendix

List of abbreviations

ACE2	Angiotensin-converting enzyme 2
BMI	Body mass index
[redacted]	[redacted]
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
ChAdOx1	Chimpanzee adenovirus Ox1
CI	Confidence interval
COVID-19	Coronavirus disease
CT	Computerised tomography
CV	Coefficient of Variation
CVST	Cerebral Venous Sinus Thrombosis
CVT	Cerebral Venous Thrombosis
DCO1	Data cut-off 1,04 November 2020
DCO2	Data cut-off 2,07 December 2020
DIC	Disseminated Intravascular Coagulation
DNA	Deoxyribonucleic acid
DVT	Deep Vein Thrombosis
EEA	European Economic Area
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunospot
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FiO_2	Fraction of inspired Oxygen
FVS-1	Fully Vaccinated Analysis Set-1 (participants who were enrolled in Study D8111C00002 before the temporary interruption [September 7, 2020] and received 2 doses of the study vaccine with no major protocol deviation.)
FVS-2	Fully Vaccinated Analysis Set-2 (participants who received 2 doses of the study vaccine with no major protocol deviation in Study D8111C00002)
GMT	Geometric mean titer
GFP	Green fluorescent protein
gRNA	Genomic RNA
HCoV	Human coronavirus
HEK293 cells	Human embryonic kidney 293 cells
HIT	Heparin-Induced Thrombocytopenia
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
ifu	Infectious units
IFN-γ	Interferon-gamma
IgG	Immunoglobulin G
IL-2/4/5/6/10/13/18	Interleukin 2/4/5/6/10/13/18
ITT	Intent-to-treat
LD	Low Dose
LDLD	Low Dose Low Dose
LDSD	Low Dose Standard Dose
LLoQ	Lower Limit of Quantification
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East respiratory syndrome coronavirus
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger RNA
MVM	Minute virus of mouse
MVS	Master Virus Seed
PBS	Phosphate buffered saline
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PE	Pulmonary Embolism
PFU	Plaque-forming unit
PO_2	Partial pressure of oxygen
PRNT	Plaque Reduction Neutralisation Test
qPCR	Quantitative polymerase chain reaction
RBD	Receptor binding domain
RCA	Replication competent adenovirus
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcription PCR
SARS	Severe acute respiratory syndrome
SARS-CoV	Severe Acute Respiratory Syndrome CoronaVirus
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus-2
SD	Standard Dose
SDSD	Standard Dose Standard Dose
S protein	Spike protein
S1	Amino-terminal region of the S protein, containing RBD
S2	Carboxy-terminal region of the S protein, containing the transmembrane region
SFC	Spot forming cell
sgRNA	Subgenomic RNA
SMQ	Standardised MedDRA queries
SpO_2	Saturation of percutaneous Oxygen
SV40	Simian Virus 40
TCID	Tissue Culture Infective Dose
TetR	Tet repressor

Th1/2	T helper cell type 1/2
TMA	Transcription-mediated amplification
TNF-α	Tumor necrosis factor-alpha
TVS	Total Vaccinated Analysis Set
tPA	The human tissue plasminogen activator
UV	Ultraviolet
VE	Vaccine efficacy
vp	Viral particles
WCB	Working cell bank
WHO	World Health Organization
WVS	Working Virus Seed
PMDA	Pharmaceuticals and Medical Devices Agency
X days after vaccination	Day X from the day after vaccination to (e.g., “2 days after vaccination” refers to 2 days after the date of vaccination)
For X days after vaccination	For X days from the day after vaccination (e.g., “for 2 days after vaccination” refers to 3 days from the date of vaccination to 2 days after the date of vaccination)
Vaxzevria	Vaxzevria Intramuscular Injection, coronavirus (SARS-CoV-2) vaccine (recombinant chimpanzee adenovirus vector)