WHO SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vaxzevria, solution for injection in multidose container
COVID-19 Vaccine (ChAdOx1-S [recombinant]).

The vaccine fulfils WHO requirements for COVID-19 vaccine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:
COVID-19 Vaccine (ChAdOx1-S* recombinant), not less than 2.5×10^8 infectious units (Inf.U), which corresponds to 5×10^{10} viral particles (vp).

*Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. Produced in genetically modified human embryonic kidney (HEK) 293 cells.

This product contains genetically modified organisms (GMOs).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is colourless to slightly brown, clear to slightly opaque and particle free with a pH of 6.6.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vaxzevria is indicated for active immunisation of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19) (see sections 4.4 and 5.1).

The use of the vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Vaxzevria should be administered by a trained healthcare professional.

Posology

The Vaxzevria primary vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose (see section 5.1).

It is recommended that individuals who receive a first dose of Vaxzevria complete the primary vaccination course with Vaxzevria (see section 4.4).

A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with Vaxzevria or an mRNA COVID-19 vaccine (see sections 4.8 and 5.1). The third dose should be administered at least 3 months after completing the primary vaccination course.

Elderly population
No dosage adjustment is required in elderly individuals ≥65 years of age.

Paediatric population
The safety and efficacy of Vaxzevria in children and adolescents (aged <18 years old) have not yet been established. No data are available.

Method of administration

Vaxzevria is for intramuscular (IM) injection only, preferably in the deltoid muscle.

For instructions on administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity including anaphylaxis

Hypersensitivity reactions including anaphylaxis and angioedema have occurred following administration of Vaxzevria.

Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination. An additional dose of the vaccine should not be given to those who have experienced a severe hypersensitivity reaction to a previous dose of Vaxzevria.

Concurrent illness

As with other vaccines, administration of Vaxzevria should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as cold, and/or low-grade fever should not delay vaccination.

Thromboembolism and thrombocytopenia

A very rare and serious combination of thrombosis and thrombocytopenia including thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed following vaccination with Vaxzevria during post-authorisation use. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. The majority of the events occurred within the first 21 days following vaccination and some events had a fatal outcome. The reporting rates after the second dose are lower compared to after the first dose. See also section 4.3.

Whilst specific risk factors for thromboembolism in combination with thrombocytopenia have not been identified, cases have occurred in patients with a previous history of thrombosis, as well as in patients with autoimmune disorders, including immune thrombocytopenia. The benefits and risks of vaccination should be considered in these patients.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and thrombocytopenia, as well as coagulopathies. Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms such as a severe or persistent headaches, blurred vision, confusion, seizures, shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain or unusual skin bruising and or petechia a few days after vaccination.

Individuals diagnosed with thrombocytopenia within 21 days of vaccination with Vaxzevria, should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 21 days of vaccination should be evaluated for thrombocytopenia.

Healthcare professionals should consult applicable guidance and, if available, seek advice from specialists (e.g. haematologists, specialists in coagulation) to diagnose and treat this condition.

Events of cerebrovascular venous and sinus thrombosis without thrombocytopenia have been reported very rarely following vaccination with Vaxzevria, although a causal relationship has not been established. These events can be fatal and may require different treatment approaches than TTS. Healthcare professionals should consult applicable guidance.

Risk of bleeding with intramuscular administration

As with other intramuscular injections, Vaxzevria should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to persons on anticoagulation therapy, because bleeding or bruising may occur following an intramuscular administration in these individuals.

Neurological events

Very rare events of demyelinating disorders, including Guillain-Barré syndrome (GBS), have been reported following vaccination with Vaxzevria. A causal relationship has not been established.
As with other vaccines, the benefits and potential risks of vaccinating individuals with Vaxzevria should be considered.

Risk of very rare events after a booster dose

The risk of very rare events (such as coagulation disorders including thrombosis with thrombocytopenia syndrome) after a booster dose of Vaxzevria has not yet been characterised.

Immunocompromised individuals

It is not known whether individuals with impaired immune responsiveness, including individuals receiving immunosuppressant therapy, will elicit the same response as immunocompetent individuals to the vaccine regimen.

Duration and level of protection

The duration of protection has not yet been established.
As with any vaccine, vaccination with Vaxzevria may not protect all vaccine recipients.

Interchangeability

There are limited safety, immunogenicity and efficacy data available regarding the interchangeability of Vaxzevria with other COVID-19 vaccines. For the available data on the use of Vaxzevria as a booster dose following primary vaccination with another COVID-19 vaccine, see sections 4.8 and 5.1.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, and is considered to be essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

The safety, immunogenicity and efficacy of co-administration of Vaxzevria with other vaccines have not been evaluated.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data from more than 400 case reports of pregnant women or women who became pregnant after receiving Vaxzevria do not suggest unusual patterns of pregnancy complications or foetal/neonatal outcomes. No increased risk of maternal thrombosis in combination with thrombocytopenia has been observed.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3).

Use of Vaxzevria may be considered during pregnancy when the benefits of vaccination outweigh the potential risks.

Breastfeeding

Anti-SARS-CoV-2 S antibodies are excreted in breast milk of mothers vaccinated with Vaxzevria. In animal studies, lactational transfer of anti-SARS-CoV-2 S antibodies from maternal female mice to pups was observed (see section 5.3). It is unknown whether the vaccine itself is excreted in human milk. In animal studies no quantifiable levels of the vaccine were detected in the mammary gland in female mice.

Available non-clinical, clinical and post-marketing data do not suggest a risk to breastfed newborns/infants.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Vaxzevria has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Primary vaccination course

The overall safety of Vaxzevria is based on an analysis of pooled data from four clinical trials conducted in the United Kingdom, Brazil, and South Africa. At the time of analysis, 24,244 participants ≥18 years old had been randomised and received either Vaxzevria or control. Out of these, 12,282 received at least one dose of Vaxzevria, with a median duration of follow-up of 4.5 months.

Demographic characteristics were generally similar among participants who received Vaxzevria and those who received control. Overall, among the participants who received Vaxzevria, 89.8% were

aged 18 to 64 years and 10.2% were 65 years of age or older. The majority of recipients were White (75.5%), 9.8% were Black and 3.7% were Asian; 55.8% were female and 44.2% male.

The most frequently reported adverse reactions were injection site tenderness (>60%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%); and arthralgia, nausea (>20%). The majority of adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination.

Following vaccination, recipients may experience multiple adverse reactions occurring at the same time (for example, myalgia/arthralgia, headache, chills, pyrexia and malaise). If a recipient reports persistent symptoms, alternative causes should be considered.

When compared with the first dose, adverse reactions reported after the second dose were milder and reported less frequently.

Adverse reactions were generally milder and reported less frequently in older adults (≥65 years old).

The safety of Vaxzevria was also assessed in a phase III clinical trial conducted in the United States, Peru and Chile. At the time of the analysis, 32,379 participants ≥18 years old had been randomised and of these, 21,587 participants received at least one dose of Vaxzevria and 20,769 received two doses. The safety profile observed in this phase III study was consistent with the established safety profile for Vaxzevria.

Booster dose (third dose)

The safety profile observed in individuals who received a booster dose (third dose) was consistent with the known safety profile of Vaxzevria. No new safety concerns, as compared with adverse reactions reported for the primary vaccination course with Vaxzevria, have been identified in individuals receiving a booster dose of Vaxzevria.

Booster dose (third dose) following primary vaccination with Vaxzevria

In study D7220C00001, 367 participants who had previously received a 2-dose primary vaccination course with Vaxzevria received a single booster dose (third dose) of Vaxzevria. Median time between the second dose and the booster dose was 8.6 months (263 days).

The most frequently reported adverse reactions in previously Vaxzevria vaccinated participants were injection site tenderness (54%), fatigue (43%), injection site pain (38%), headache (34%), myalgia (23%), and malaise (22%). The majority of these adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination.

Booster dose (third dose) following primary vaccination with an approved mRNA COVID-19 vaccine

In study D7220C00001, 322 participants who had previously received a 2-dose primary vaccination course with an approved COVID-19 mRNA vaccine received a single booster dose (third dose) of Vaxzevria. Median time between the second dose and the booster dose was 3.9 months (119 days).

The most frequently reported adverse reactions in previously mRNA vaccinated participants were injection site tenderness (71%), fatigue (58%), headache (52%), injection site pain (50%), myalgia (47%), malaise (42%), chills (31%), and nausea (21%). The majority of these adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination.

Analgesic and/or anti-pyretic medicinal products (e.g. paracetamol-containing products) may be used to provide symptomatic relief from post-vaccination adverse reactions.

Tabulated list of adverse reactions

The safety profile presented below is based on an analysis of pooled data from four clinical trials conducted in the United Kingdom, Brazil, and South Africa which included 24,244 participants ≥18 years old and from post-authorisation experience.

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Table 1 Adverse drug reactions

MedDRA SOC	**Frequency**	**Adverse Reactions**
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy[a]
	Very rare	Thrombocytopenia[b]
Immune system disorders	Not known	Anaphylactic reaction[c]
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness[a] Somnolence[a] Paraesthesia[d] Hypoaesthesia[d]
Ear and labyrinth disorders	Uncommon	Tinnitus
Vascular disorders	Very rare	Thrombosis in combination with thrombocytopenia*
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting Diarrhoea[a]
	Uncommon	Abdominal pain[a]
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis[a] Pruritus[a] Rash[a] Urticaria[a]
	Not known	Angioedema[c]
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
	Common	Pain in extremity[a]
General disorders and administration site conditions	Very common	Injection site tenderness Injection site pain Injection site warmth Injection site pruritus Fatigue Malaise Pyrexia[e]Chills
	Common	Injection site swelling Injection site erythema Influenza-like illness[a]

[a] Unsolicited adverse reactions.

[b] The majority of reported events occurred in individuals aged 18-59 years old.

[c] Identified from post-authorisation experience.

[d] The adverse reaction was identified during post-marketing. Many of these events were co-reported with reactogenecity events.

[e] Pyrexia includes feverishness (very common) and fever ≥38°C (common).

*A very rare and serious combination of thrombosis and thrombocytopenia including thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed with a frequency less than 1/100,000. This includes cases presenting as venous thrombosis, including unusual sites such

as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system or www.covax.azcovid-19.com.

4.9 Overdose

Experience of overdose is limited.
There is no specific treatment for an overdose with Vaxzevria. In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccine, other viral vaccines, ATC code: J07BX03

Mechanism of action

Vaxzevria is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralising antibody and cellular immune responses.

Clinical efficacy

Analysis of data from Study D8110C00001

The clinical efficacy of Vaxzevria has been evaluated based on an analysis of Study D8110C00001: a randomised, double-blinded, placebo-controlled phase III study conducted in the United States, Peru and Chile. The study excluded participants with severe and/or uncontrolled cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic disease, and neurological illnesses; as well as those with severe immunosuppression, pregnant women and participants with a known history of SARS-CoV-2 infection. All participants are planned to be followed for up to 12 months, for assessments of efficacy against COVID-19 disease.

Participants ≥18 years of age received two doses (5×10^{10} vp per dose) of Vaxzevria (N=17,662) or saline control (N=8,550), administered via IM injection on Day 1 and Day 29 (-3 to +7 days). The median dose interval was 29 days and the majority of participants (95.7% and 95.3% for Vaxzevria and control, respectively) received the second dose ≥26 to ≤36 days after dose 1.

Baseline demographics were well balanced across Vaxzevria and the control groups. Of the participants who received Vaxzevria, 79.1% were aged 18 to 64 years (with 20.9% aged 65 or older) and 43.8% of subjects were female. Of those randomised, 79.3% were White, 7.9% were Black, 4.2% were Asian, 4.2% were American Indian or Alaska Native. A total of 10,376 (58.8%) participants had at least one pre-existing comorbidity, defined as; chronic kidney disease, chronic obstructive pulmonary disease, lower immune health because of a solid organ transplant, history of obesity (BMI >30), serious heart conditions, sickle cell disease, type 1 or 2 diabetes, asthma, dementia, cerebrovascular diseases, cystic fibrosis, high blood pressure, liver disease, pulmonary fibrosis,

thalassemia or history of smoking. At the time of analysis the median follow-up time post-dose 2 was 61 days.

Final determination of COVID-19 cases were made by an adjudication committee. Overall vaccine efficacy, efficacy in older adults ≥65 years old and vaccine efficacy against severe or critical COVID-19 are presented in Table 2.

Table 2 Vaxzevria efficacy against COVID-19 in Study D8110C00001

	Vaxzevria		Control		Vaccine efficacy % (95% CI)
	N	Number of COVID-19 cases[a], n (%)	N	Number of COVID-19 cases[a], n (%)	
Symptomatic COVID-19 illness	17,662	73 (0.4)	8,550	130 (1.5)	74.0 (65.3, 80.5)
Age ≥65 years old	3,696	5 (0.1)	1,812	14 (0.8)	83.5 (54.2, 94.1)
Severe or critical symptomatic COVID-19 illness[b]	17,662	0 (0.0)	8,550	8 (<0.1)	100.0 (71.6, NE)[c]

N = Number of subjects included in each group; n = Number of subjects having a confirmed event;
CI = Confidence Interval; NE = Not Evaluable.

[a] Positive RT-PCR confirmed SARS-CoV-2 and at least one of the following symptoms from Category A: Pneumonia diagnosed by chest x-ray, or CT scan, oxygen saturation of ≤94% on room air or requiring either new initiation or escalation in supplemental oxygen, new or worsening dyspnoea/shortness of breath; or two or more symptoms from Category B: fever (defined as >100°F (≥37.8°C) or feverishness), new or worsening cough, myalgia/muscle pain, fatigue that interferes with daily activities, vomiting and/or diarrhoea, or anosmia (loss of smell), or ageusia (loss of taste). Confirmed by adjudication committee.

[b] Key secondary endpoint; severe COVID-19 was defined based on laboratory-confirmed COVID-19, plus any of the following: clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥125 beats per minute, oxygen saturation ≤93% on room air at sea level, or partial pressure of oxygen to fraction of inspired oxygen ratio <300 mmHg); or respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation), evidence of shock (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg or requiring vasopressors); or significant acute renal, hepatic, or neurological dysfunction; or admission to an intensive care unit, or death.

[c] 97.5% CI.

In the pre-specified primary efficacy analysis, based on 190 adjudicated cases, there were 65 (0.4%) COVID-19 cases in participants receiving Vaxzevria (N=17,817) and 125 (1.5%) COVID-19 cases in participants receiving placebo (N=8,589), with a vaccine efficacy of 76.0% (95% CI: 67.6; 82.2).

In individuals with or without prior evidence of SARS-CoV-2 infection, the vaccine efficacy of Vaxzevria (≥15 days post-dose 2) was 73.7% (95% CI: 63.1; 80.1); 76 (0.4%) vs 135 (1.5%) cases of COVID-19 for Vaxzevria (N=18,563) and control (N=9,031), respectively.

When cumulative incidence of viral shedding was examined (≥15 days post-dose 2), time to clearance of SARS-CoV-2 in saliva samples in Vaxzevria participants was notably shorter (11 vs 16 days).

Evaluation of the post-treatment response for SARS-CoV-2 nucleocapsid antibodies in participants who had received two doses of Vaxzevria (≥15 days post-dose 2) as compared to placebo, showed there were 156 (0.9%; N=17,662) vs 202 (2.4%; N=8,550) cases of COVID-19, respectively. Corresponding to a vaccine efficacy of 64.3% (95% CI: 56.1; 71.0).

Participants with one or more comorbidities who received Vaxzevria (≥15 days post-dose 2) had an efficacy of 75.2% (95% CI: 64.2; 82.9) and participants without comorbidities had a vaccine efficacy of 71.8% (95% CI: 55.5, 82.1).

Primary analysis of pooled data from COV001, COV002, COV003, and COV005

Vaxzevria has been evaluated based on pooled data from four on-going randomised, blinded, controlled trials: a Phase I/II Study, COV001, in healthy adults 18 to 55 years of age in the UK; a Phase II/III Study, COV002, in adults ≥18 years of age (including the elderly) in the UK; a Phase III Study, COV003, in adults ≥18 years of age (including the elderly) in Brazil; and a Phase I/II study, COV005, in adults aged 18 to 65 years of age in South Africa. The studies excluded participants with severe and/or uncontrolled cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic disease, and neurological illnesses; as well as those with severe immunosuppression. All participants are planned to be followed for up to 12 months, for assessments of safety and efficacy against COVID-19 disease.

In the pooled analysis for efficacy, participants ≥18 years of age received two doses of Vaxzevria (N=8,597) or control (meningococcal vaccine or saline) (N=8,581). Participants randomised to Vaxzevria received either two standard doses [SD] (5×10^{10} vp per dose) or one low dose [LD] (2.2×10^{10} vp) followed by one SD (5×10^{10} vp), administered via IM injection. Overall, the majority of participants (83.8%) received two SD.

Because of logistical constraints, the interval between dose 1 and dose 2 ranged from 3 to 28 weeks, with 77.0% of participants receiving their two doses within the interval of 4 to 12 weeks.

Baseline demographics were well balanced across Vaxzevria and control treatment groups. In the pooled analysis, among the participants who received Vaxzevria, 91.8% of participants were 18 to 64 years old (with 8.2% aged 65 or older); 56.0% of subjects were female; 74.9% were White, 3.7% were Asian, and 10.1% were Black. A total of 3,056 (35.5%) participants had at least one pre-existing comorbidity (defined as a BMI ≥30 kg/m^2, cardiovascular disorder, respiratory disease or diabetes). At the time of primary analysis the median follow-up time post-dose 1 and post-dose 2 was 4.7 months and 2.7 months, respectively.

Final determination of COVID-19 cases were made by an adjudication committee, who also assigned disease severity according to the WHO clinical progression scale. A total of 332 participants had SARS-CoV-2 virologically confirmed COVID-19 occurring ≥15 days post second dose with at least one COVID-19 symptom (objective fever (defined as ≥37.8°C), cough, shortness of breath, anosmia, or ageusia) and were without evidence of previous SARS-CoV-2 infection. Vaxzevria significantly decreased the incidence of COVID-19 compared to control (see Table 3).

Table 3 Vaxzevria efficacy against COVID-19[a] in COV001, COV002, COV003 and COV005

Population	Vaxzevria		Control		Vaccine efficacy % (95% CI)
	N	Number of COVID-19 cases[b], n (%)	N	Number of COVID-19 cases[b], n (%)	
Primary analysis population					
Overall (SDSD + LDSD)	8,597	84 (0.98)	8,581	248 (2.89)	66.73 (57.41, 74.01)
Licensing regimen					
SDSD	7,201	74 (1.03)	7,179	197 (2.74)	63.09 (51.81, 71.73)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval; LD = Low dose; SD = Standard dose

[a] Primary study endpoint was based on confirmed COVID-19 cases in subjects aged 18 years and over who were seronegative at baseline, who had received two doses (SDSD or LDSD) and were on-study ≥15 days post second dose.

[b] Virologically confirmed SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥37.8°C), cough, shortness of breath, anosmia, or ageusia. Confirmed by adjudication committee.

The level of protection gained from one SD of Vaxzevria was assessed in an exploratory analysis that included participants who had received one dose of SD. Participants were censored from the analysis at the earliest time point of when they received a second dose or at 12 weeks post-dose 1. In this population, vaccine efficacy from 22 days post-dose 1 was 71.42% (95% CI: 51.11; 84.08 [Vaxzevria 18/9,335 vs control 63/9,312]).

Exploratory analyses showed that increased vaccine efficacy was observed with increasing dose interval, see Table 4.

Table 4 Vaxzevria efficacy by dosing interval[a] in COV001, COV002, COV003 and COV005

Dosing interval	Vaxzevria		Control		Vaccine efficacy % (95% CI)
	N	Number of COVID-19 cases[b], n (%)	N	Number of COVID-19 cases[b], n (%)	
<6 weeks	3,905	35 (0.90)	3,871	76 (1.96)	55.09 (32.99, 69.90)
6-8 weeks	1,124	20 (1.78)	1,023	44 (4.30)	59.72 (31.68, 76.25)
9-11 weeks	1,530	14 (0.92)	1,594	52 (3.26)	72.25 (49.95, 84.61)
≥12 weeks	2,038	15 (0.74)	2,093	76 (3.63)	79.99 (65.20, 88.50)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval; LD = Low dose; SD = Standard dose

[a] Primary study endpoint was based on confirmed COVID-19 cases in subjects aged 18 years and over who were seronegative at baseline, who had received two doses (SDSD or LDSD) and were on-study ≥15 days post second dose.

[b] Virologically confirmed SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥37.8°C), cough, shortness of breath, anosmia, or ageusia. Confirmed by adjudication committee.

Efficacy against COVID-19 hospital admission and severe COVID-19 disease

Vaxzevria reduced COVID-19 hospitalisation (WHO Severity grading ≥4).

In participants who had received two doses of Vaxzevria (SDSD + LDSD, ≥15 days post-dose 2) as compared to control, there were 0 (N=8,597) vs 9 (0.10%; N=8,581) cases of hospitalised COVID-19, respectively. Corresponding to a vaccine efficacy of 100% (97.5% CI: 50.19; Not Evaluable).

In all participants who received SD as a first dose, as from 22 days post-dose 1, the vaccine efficacy was 100% (97.5% CI: 69.92; Not Evaluable) with 0 (N=9,335) cases of COVID-19 hospitalisation in participants who received Vaxzevria, when compared to 14 (0.15%, N=9,312) cases reported for control. Two of the COVID-19 cases reported for control (≥22 days post-dose 1) were severe (WHO severity grading ≥6).

Efficacy against COVID-19 in subgroups

Participants who had one or more comorbidities had a vaccine efficacy of 62.71% [95% CI: 44.79; 74.82]; 34 (1.11%) vs 93 (3.00%) cases of COVID-19 for Vaxzevria (SDSD + LDSD, ≥15 days post-dose 2, N=3,056) and control (N=3,102), respectively; which was similar to the vaccine efficacy observed in the overall population.

In participants ≥65 years old who had received 2 doses of Vaxzevria (SDSD + LDSD, ≥15 days post-dose 2, N=703), there were 4 cases of COVID-19 compared to 8 cases for control (N=680), corresponding to a vaccine efficacy of 51.91% (95% CI: -59.98, 85.54). A large proportion (89.6%) of older adults received their second dose <6 weeks after their first. In older adults (≥65 years old) who

had received SD as a first dose (≥22 days post-dose 1), there were 6 cases of COVID-19 for Vaxzevria (N=945) compared to 13 for control (N=896), with 0 vs 2 cases in the Vaxzevria and control groups, respectively, leading to hospitalisation (WHO severity grading ≥4).

Immunogenicity

Primary analysis of pooled data from COV001, COV002, COV003, and COV005

Following vaccination with Vaxzevria, in participants who were seronegative at baseline, seroconversion (as measured by a ≥4-fold increase from baseline in S-binding antibodies) was demonstrated in ≥98% of participants at 28 days after the first dose and >99% at 28 days after the second. Higher S-binding antibodies were observed with increasing dose interval (Table 5).

Generally similar trends were observed between analyses of neutralising antibodies and S-binding antibodies. An immunological correlate of protection has not been established; therefore the level of immune response that provides protection against COVID-19 is unknown.

Table 5 SARS CoV-2 S-binding antibody response to Vaxzevria (SDSD)[a]

Population	Baseline[b]	28 days after dose 1	28 days after dose 2
	GMT (95% CI)	**GMT (95% CI)**	**GMT (95% CI)**
Overall	(N=1,538) 57.1 (53.8; 60.6)	(N=1,466) 8,358.0 (7,879.2; 8,866.0)	(N=1,511) 30,599.8 (29,137.1; 32,135.9)
Dose Interval			
<6 weeks	(N=578) 61.4 (55.3; 68.0)	(N=578) 8,184.5 (7,423.9; 9,023.1)	(N=564) 21,384.2 (19,750.7; 23,152.8)
6-8 weeks	(N=339) 56.1 (49.6; 63.3)	(N=290) 9,103.9 (8,063.1; 10,279.1)	(N=331) 28,764.8 (25,990.8; 31,834.9)
9-11 weeks	(N=331) 53.6 (47.5; 60.4)	(N=309) 8,120.9 (7,100.2; 9,288.4)	(N=327) 37,596.1 (34,494.2; 40,976.8)
≥12 weeks	(N=290) 54.3 (47.6; 61.9)	(N=289) 8,249.7 (7,254.5; 9,381.4)	(N=289) 52,360.9 (47,135.2; 58,165.9)

N = Number of subjects included in each group; GMT = Geometric mean titre; CI = Confidence interval; S = Spike

[a] Immune response evaluated using a multiplex immunoassay.

[b] Individuals were seronegative at baseline.

The immune response observed in participants with one or more comorbidities was consistent with the overall population.

High seroconversion rates were observed in older adults (≥65 years) after the first SD (97.3% [N=149, 95% CI: 93.3; 99.3]) and the second SD (100.0% [N=156, 95% CI: 97.7; Not Evaluable]). The majority of older adults had a dose interval of <6 weeks. The increase in S-binding antibodies for older adults with a dose interval of <6 weeks (28 days after second SD: GMT=18,759.6 [N=126, 95% CI: 15,764.8; 22,323.3]) was comparable to all participants who received their second dose after an interval of <6 weeks (see Table 5).

In participants with serological evidence of prior SARS-CoV-2 infection at baseline (GMT=10,979.1 [N=36; 95% CI: 6,452.7; 18,680.5]), S-antibody titres peaked 28 days after dose 1 (GMT=139,010.4 [N=35; 95% CI: 95,429.0; 202,495.1]) but did not increase further after the second dose.

Spike-specific T cell responses as measured by IFN-ɣ enzyme-linked immunospot (ELISpot) assay are induced after a first dose of Vaxzevria. Geometric mean responses are generally similar across age strata and regardless of presence of comorbidity. These do not rise further after a second dose. Th1 cytokines are induced by Vaxzevria with cells expressing IFN-γ, IL-2, and/or TNFα which are generally similar between age categories.

Study D7220C00001, immunogenicity of a booster dose (third dose) following primary vaccination with Vaxzevria or an mRNA COVID-19 vaccine

D7220C00001 is a phase II/III partially double-blind, active-controlled study in which 367 participants ≥30 years old previously vaccinated with Vaxzevria and 322 participants ≥30 years old previously vaccinated with an mRNA vaccine received a single booster dose of Vaxzevria at least 90 days after receiving the second dose of their primary vaccination course. Immunogenicity was assessed in 342 participants previously vaccinated with Vaxzevria and 294 participants previously vaccinated with an mRNA vaccine, all of whom were seronegative at baseline.

The effectiveness of Vaxzevria administered as a single booster dose in participants previously vaccinated with Vaxzevria was demonstrated by evaluating non-inferiority of the immune response of pseudoneutralising antibody titres against the ancestral strain compared to that elicited by a 2-dose primary vaccination course in a subset of matched participants in study D8110C00001.

Non-inferiority for GMT ratio was demonstrated when comparing pseudoneutralising antibody titres 28 days after the booster dose to titres 28 days after the primary vaccination course (see Table 6).

Table 6 Neutralising antibody titres against the ancestral strain following booster dosing with Vaxzevria in participants previously vaccinated with Vaxzevria

	28 days after primary vaccination course with Vaxzevria[a]	**28 days after booster dose**	**GMY ratio[b]**	**Met Non-inferiority objective (Y/N)**
n	508	327	327/508	
GMT[c]	242.80	248.89	1.03	Y[d]
(95% CI)	(224.82, 262.23)	(229.53, 269.89)	(0.92, 1.15)	

n = Number of subjects in analysis; GMT = Geometric mean neutralising antibody titre; CI = Confidence interval; GMT Ratio = Geometric mean titre ratio

[a.] Based on analyses from a matched cohort of participants in study D8110C00001.

[b.] GMT 28 days after booster dose to GMT 28 days after the second dose of the primary vaccination course.

[c.] Reported results have been adjusted using an ANCOVA model including fixed-effect terms for visit window, time since previous vaccination (for booster), baseline comorbidities, sex, age and a random subject effect.

[d.] Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the GMT ratio of the comparator group and the reference group is >0.67.

Vaxzevria was also shown to be effective in eliciting antibody responses in participants who had previously received primary vaccination with an mRNA vaccine. In these participants, a single booster dose of Vaxzevria resulted in increased humoral responses, with geometric mean fold rise (GMFR) of 3.77 (95% CI: 3.26, 4.37) in neutralising antibody titres against the ancestral strain from pre-booster to 28 days after the booster dose.

Paediatric population

The safety and efficacy of Vaxzevria in children and adolescents (aged <18 years old) have not yet been established. No data are available.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Toxicity and local tolerance studies

In a repeat-dose toxicity study in mice, IM administration of Vaxzevria was well tolerated. Non-adverse, mixed and/or mononuclear cell inflammation was observed in the subcutaneous tissues and skeletal muscle of the administration sites and adjacent sciatic nerve consistent with the anticipated findings after IM injection of vaccines. There were no findings in the administration sites or sciatic nerves at the end of the recovery period, indicating complete recovery of the Vaxzevria-related inflammation.

Mutagenicity and carcinogenicity

Vaxzevria is a vaccine, as such, genotoxicity (mutagenicity) and carcinogenicity studies have not been conducted.

Reproductive toxicity

Biodistribution studies conducted in mice did not show measurable distribution of Vaxzevria to the gonads (testes, ovaries) following IM injection.
In a reproductive and development toxicity study, Vaxzevria did not induce maternal or developmental toxicity following maternal exposure during the pre-mating, gestation or lactating periods. In this study, vaccine elicited detectable anti-SARS-CoV-2 S-glycoprotein maternal antibodies were transferred to the foetuses and pups, indicating placental and lactational transfer, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine hydrochloride monohydrate
Magnesium chloride hexahydrate
Polysorbate 80
Ethanol
Sucrose
Sodium chloride
Disodium edetate dihydrate
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this vaccine must not be mixed with other medicinal products.

6.3 Shelf life

Unopened multidose vial

6 months

The following information is intended to guide healthcare professionals only in case of an unforeseen temporary temperature excursion. It is not a recommended storage or shipping condition.

The shelf-life of unopened vials includes the following unforeseen excursions from refrigerated storage (2°C – 8°C) for a single period of:
- 12 hours up to 30°C
- 72 hours down to -3°C

Unopened vials must always be returned to refrigerated storage (2°C – 8°C) following an unforeseen temperature excursion.

The occurrence of an unforeseen temperature excursion for unopened vials does not impact how the vials should be stored after first opening (first vial puncture).

Opened multidose vial

Use as soon as practically possible and within 6 hours.
The vaccine should be stored between 2°C and 8°C during the in-use period.

6.4 Special precautions for storage

Unopened multidose vial

Store at 2-8°C.
Do not freeze.
Keep vials in outer carton to protect from light.

Opened multidose vial

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Multidose vial

5 ml of solution in a 10-dose vial (clear type I glass) with stopper (elastomeric with aluminium overseal). Packs of 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Administration

Vaxzevria is a colourless to slightly brown, clear to slightly opaque solution. The vaccine should be inspected visually for particulate matter and discolouration prior to administration. Discard the vial if the solution is discoloured or visible particles are observed. Do not shake the vial.

Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection to be administered intramuscularly. Use a separate sterile needle and syringe for each individual.

Each vial contains at least the number of doses stated. It is normal for liquid to remain in the vial after withdrawing the final dose. When low dead volume syringes and/or needles are used, the amount remaining in the vial may be sufficient for an additional dose. Care should be taken to ensure a full 0.5 ml dose is administered. Where a full 0.5 ml dose cannot be extracted, the remaining volume should be discarded. Do not pool excess vaccine from multiple vials.

The vaccine does not contain any preservative. After first dose withdrawal, use the vial as soon as practically possible and within 6 hours (stored at 2°C to 8°C). Discard any unused vaccine.

To facilitate the traceability of the vaccine, the name and the batch number of the administered product should be clearly recorded for each recipient.

Disposal

Vaxzevria contains genetically modified organisms (GMOs). Any unused vaccine or waste material should be disposed of in accordance with local requirements. Spills should be disinfected with an appropriate antiviral disinfectant.

7. MARKETING AUTHORISATION HOLDER / EMERGENCY USE APPROVAL HOLDER OR EQUIVALENT

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)/ EMERGENCY USE APPROVAL OR EQUIVALENT

9. DATE OF FIRST AUTHORISATION

Date of first authorisation: 15 February 2021

10. DATE OF REVISION OF THE TEXT

November 2022