▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vaxzevria, suspension for injection
COVID 19 Vaccine (ChAdOx1 S [recombinant])

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)

*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).

Excipient with known effect

Each dose (0.5 ml) contains approximately 2 mg of ethanol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection.

The suspension is colourless to slightly brown, clear to slightly opaque with a pH of 6.6.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vaxzevria is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals ≥18 years old.

The use of Vaxzevria should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 18 years of age and older
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).

A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with Vaxzevria. The third dose should be administered at least 3 months after completing the primary vaccination course (see sections 4.4, 4.8 and 5.1).

Elderly population
No dosage adjustment is required. See also sections 4.4 and 5.1.

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.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

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.

Individuals who have experienced thrombosis with thrombocytopenia syndrome (TTS) following vaccination with Vaxzevria (see section 4.2).

Individuals who have previously experienced episodes of capillary leak syndrome (see also section 4.4).

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.
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.

Anxiety-related reactions
Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

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

Coagulation disorders

Thrombosis with thrombocytopenia syndrome
Thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed very rarely following vaccination with Vaxzevria. This includes severe 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. Some cases had a fatal outcome. The majority of these cases occurred within the first 3 weeks following vaccination but have also been reported after this period. The reporting rates have been lower after the second dose than after the first dose. Risk factors have not been identified. Some cases had increased D-dimer levels >4000ng/ml, positive platelet factor 4 antibodies and/or laboratory evidence of platelet activation.

As a precautionary measure, administration of the Vaxzevria in patients with a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2) or cerebral venous sinus thrombosis should only be considered when the benefit outweighs any potential risks.

TTS requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

Cerebrovascular venous and sinus thrombosis: Events of cerebrovascular venous and sinus thrombosis without thrombocytopenia have been observed very rarely following vaccination with Vaxzevria. Some cases had a fatal outcome. The majority of these cases occurred within the first four weeks following vaccination. This information should be considered for individuals at increased risk for cerebrovascular venous and sinus thrombosis. These events may require different treatment approaches than TTS and healthcare professionals should consult applicable guidance.

Thrombocytopenia
Cases of thrombocytopenia, including immune thrombocytopenia (ITP), have been reported after receiving Vaxzevria, typically within the first four weeks after vaccination. Very rarely, these presented with very low platelet levels (<20,000 per µL) and/or were associated with bleeding. Cases with fatal outcome have been reported. Some cases occurred in individuals with a history of immune thrombocytopenia. If an individual has a history of a thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before administering the vaccine and platelet monitoring is recommended after vaccination.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Vaccinated individuals should be instructed to seek immediate medical attention if four or more days after vaccination they develop new onset or worsening severe or persistent headaches with blurred vision, which do not respond to simple painkillers, or if they develop new symptoms such as shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain, any neurological symptoms or signs such as confusion or seizures, or if they experience spontaneous bleeding, unusual skin bruising and/or petechiae beyond the site of vaccination.

Individuals diagnosed with thrombocytopenia within 3 weeks after vaccination with Vaxzevria should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia.

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.

Capillary leak syndrome
Very rare cases of capillary leak syndrome (CLS) have been reported in the first days after vaccination with Vaxzevria. A history of CLS was apparent in some of the cases. Fatal outcome has been reported. CLS is a rare disorder characterised by acute episodes of oedema mainly affecting the limbs, hypotension, haemoconcentration and hypoalbuminaemia. Patients with an acute episode of CLS following vaccination require prompt recognition and treatment. Intensive supportive therapy is usually warranted. Individuals with a known history of CLS should not be vaccinated with this vaccine. See also section 4.3.

Neurological events
Guillain-Barré Syndrome (GBS) has been reported very rarely following vaccination with Vaxzevria. Healthcare professionals should be alert of GBS signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment, and to rule out other causes.

Extremely rare cases of acute disseminated encephalomyelitis (ADEM) have been reported following Vaxzevria, although a causal relationship has not been established. Cases with fatal outcome have been reported. Healthcare professionals should be alert to signs and symptoms of brain and spinal cord inflammation (uni- or bi-lateral weakness in the extremities, numbness or tingling, changes in mental state or level of consciousness, visual impairment, or seizures).

Extremely rare cases of transverse myelitis have been reported following Vaxzevria. A further dose of Vaxzevria should not be given to those who have experienced symptoms of transverse myelitis after a previous dose of this vaccine.

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

Immunocompromised individuals
The efficacy, safety and immunogenicity of the vaccine have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Vaxzevria may be lower in immunosuppressed individuals.

Duration of protection
The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness
Protection starts from approximately 3 weeks after the first dose of Vaxzevria. Individuals may not be fully protected until 15 days after the second dose is administered. As with all vaccines, vaccination with Vaxzevria may not protect all vaccine recipients (see section 5.1).

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

Ethanol
This medicinal product contains 2 mg of alcohol (ethanol) per 0.5 ml dose. The small amount of alcohol in this medicinal product will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Vaxzevria with other vaccines has not been studied (see section 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a limited experience with the use of Vaxzevria in pregnant women.

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

Administration of Vaxzevria during pregnancy should only be considered when the potential benefits outweigh any potential risks (including those described in sections 4.4 and 4.8) for the mother and foetus.

Breastfeeding
It is unknown whether Vaxzevria is excreted in human milk.

In animal studies, lactational transfer of anti-SARS-CoV-2 S antibodies from maternal female mice to pups was observed (see section 5.3).

Fertility
Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

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 phase I/II, II/III and III conducted in the United Kingdom, Brazil, and South Africa, and of data from an additional phase III clinical trial conducted in the United States, Peru and Chile. At the time of analysis, a total of 56,601 participants ≥18 years old had been randomised and of these, 33,846 participants received at least one dose of Vaxzevria and 32,030 received 2 doses.

Participants continued to be followed for safety regardless of unblinding or receipt of unblinded vaccination. For the four clinical studies performed in the United Kingdom, Brazil, and South Africa, longer follow-up of ≥12 months (median 13.0 months) from first dose is available for 10,247 participants who received Vaxzevria.

The most frequently reported adverse reactions are injection site tenderness (68%), injection site pain (58%), headache (53%), fatigue (53%), myalgia (44%), malaise (44%), pyrexia (includes feverishness (33%) and fever ≥38°C (8%)), chills (32%), arthralgia (27%) and nausea (22%). The majority of these adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination.

Very rare cases of thrombosis with thrombocytopenia syndrome have been reported post-marketing within the first three weeks following vaccination (see section 4.4).

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

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

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

The safety profile was consistent across participants with or without prior evidence of SARS-CoV-2 infection at baseline; the number of seropositive participants at baseline was 753 (3.1%).

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.

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 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.

Tabulated list of adverse reactions

The safety profile presented below is based on an analysis of data from five clinical trials which included participants ≥18 years old (pooled data from four clinical trials conducted in the United Kingdom, Brazil and South Africa, and data from one clinical trial conducted in the United States, Peru and Chile) and on data 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
	Common	Thrombocytopenia[a]
	Not known	Immune thrombocytopenia
Immune system disorders	Not known	Anaphylaxis Hypersensitivity
Metabolism and nutrition disorders	Uncommon	Decreased appetite
Nervous system disorders	Very common	Headache[b]
	Common	Dizziness
	Uncommon	Somnolence, lethargy, paraesthesia[c], hypoaesthesia[c]
	Rare	Facial paralysis[d]
	Very rare	Guillain-Barré syndrome
	Not known	Transverse myelitis
Ear and labyrinth disorders	Uncommon	Tinnitus
Vascular disorders	Very rare	Thrombosis with thrombocytopenia syndrome[e]
	Not known	Cerebrovascular venous and sinus thrombosis Capillary leak syndrome
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting, diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis, pruritus, rash, urticaria
	Not known	Angioedema, cutaneous vasculitis
Musculoskeletal and connective tissue disorders	Very common	Myalgia, arthralgia
	Common	Pain in extremity
	Uncommon	Muscle spasms
General disorders and administration site conditions	Very common	Injection site tenderness, pain, warmth, pruritus, bruising[f], fatigue, malaise, feverishness, pyrexia, chills
	Common	Injection site swelling, erythema, influenza-like illness, asthenia

[a] In clinical trials, transient mild thrombocytopenia was commonly reported (see section 4.4).
[b] Headache includes migraine (uncommon).

[c] The adverse reaction was identified during post-marketing. Many of these events were co-reported with reactogenicity events.
[d] Based on data from the clinical trial conducted in the United States, Peru and Chile. Through the safety follow-up period to 05 March 2021, facial paralysis (or palsy) was reported by five participants in the Vaxzevria group. Onset was 8 and 15 days after first dose and 4, 17, and 25 days after the second dose. All events were reported to be non-serious. No cases of facial paralysis were reported in the placebo group.
[e] Severe and very rare cases of thrombosis with thrombocytopenia syndrome have been reported post marketing. These included venous thrombosis such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis (see section 4.4).
[f] Injection site bruising includes injection site haematoma (uncommon, unsolicited adverse reaction)

Very rare events of neuroinflammatory disorders have been reported following vaccination with Vaxzevria. A causal relationship has not been established.

Post-authorisation reports of influenza-like illness
Some recipients have reported chills, shivering (in some cases rigors), and increased body temperature possibly with sweating, headache (including migraine-like headaches), nausea, myalgia and malaise, starting within a day of vaccination. These effects usually lasted for a day or two.
If a patient reports unusually high or prolonged fever, or other symptoms, alternative causes should be considered and appropriate advice should be provided for diagnostic investigation and medical management as required.

Reporting of suspected adverse reactions
If you are concerned about an adverse event, it should be reported on a Yellow Card. Reporting forms and information can be found at https://coronavirus-yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store and include the vaccine brand and batch/Lot number if available. Alternatively, adverse events of concern in association with Vaxzevria can be reported to AstraZeneca on 08000 541 028 or via www.azcovid-19.com.
Please do not report the same adverse event(s) to both systems as all reports will be shared between AstraZeneca and MHRA (in an anonymised form) and dual reporting will create unnecessary duplicates.

4.9 Overdose

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: J07BN02

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

Pooled analysis from studies COV001/COV002/COV003/COV005

Vaxzevria has been evaluated based on an interim analysis of pooled data from four 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 history of anaphylaxis or angioedema; participants with severe and/or uncontrolled cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic disease, and neurological illnesses; as well as those with immunosuppression. In studies COV001 and COV002, licensed seasonal influenza and pneumococcal vaccinations were permitted (at least 7 days before or after their study vaccine).

Based on the pre-defined criteria for interim efficacy analysis, COV002 and COV003 exceeded the threshold of ≥5 virologically confirmed COVID-19 cases per study and therefore contributed to the efficacy analysis; COV001 and COV005 were excluded.

In the pooled primary analysis for efficacy (COV002 and COV003), participants ≥18 years of age and seronegative at baseline received two doses of Vaxzevria (N=5,807) or control (meningococcal vaccine or saline) (N=5,829). Because of logistical constraints, the interval between dose 1 and dose 2 ranged from 4 to 26 weeks.

Baseline demographics were well balanced across Vaxzevria and control treatment groups. Overall, among the participants who received Vaxzevria, 94.1% of participants were 18 to 64 years old (with 5.9% aged 65 or older); 60.7% of subjects were female; 82.8% were White, 4.6% were Asian, and 4.4% were Black. A total of 2,070 (35.6%) participants had at least one pre-existing comorbidity (defined as a BMI ≥30 kg/m^2, cardiovascular disorder, respiratory disease or diabetes). The median follow-up time post-dose 1 and post-dose 2 was 132 days and 63 days, 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 131 participants had SARS-CoV-2 virologically confirmed (by nucleic acid amplification tests) COVID-19 occurring ≥15 days post-dose 2 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.

An updated efficacy analysis included 17,178 participants from all four studies. Among the participants who received Vaxzevria, 83.8% were 18 to 55 years old, 10.5% were 56 to 69 years old and 5.6% were aged 70 or older. The median follow-up time post-dose 1 and post-dose 2 was 143 days and 83 days, respectively. The results of these analyses, interim and updated efficacy analyses, are presented in Table 2.

Table 2 Vaxzevria efficacy against COVID-19

Population	Vaxzevria		Control		Vaccine efficacy % (CI)
	N	Number of COVID-19 cases, n (%)	N	Number of COVID-19 cases, n (%)	
Interim analysis (cut-off date: 04 Nov 2020)					
Primary (see above)	**5,807**		**5,829**		
COVID-19 cases		30 (0.5)		101 (1.7)	70.4 (54.8, 80.6)[a]
Hospitalisations[b]		0		5 (0.1)	-
Severe disease[c]		0		1 (<0.1)	-
Updated analysis (cut-off date: 07 Dec 2020)					
Primary (see above)	**8,597**		**8,581**		
COVID-19 cases		84 (1.0)		248 (2.9)	66.7 (57.4, 74.0)[d]
Hospitalisations[b]		0		9 (0.1)	100 (50.2, NE)[d]
Severe disease[c]		0		2 (<0.1)	-

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval; NE = Not Evaluable; [a] 95.84% CI; [b] WHO severity grading ≥4; [c] WHO severity grading ≥6; [d] 95% CI.

In the interim analysis, participants who had one or more comorbidities had a vaccine efficacy (VE) of 73.4% [95% CI: 48.5; 86.3]; 11 (0.5%) vs 43 (2.0%) cases of COVID-19 for Vaxzevria (N=2,070) and control (N=2,113), respectively; which was similar to the VE observed in the overall population. In the updated analysis, the VE in this subgroup of participants with one or more comorbidities was 62.7% (95% CI: 44.8; 74.8 [Vaxzevria 34/3,056 vs control 93/3,102]).

The number of COVID-19 cases in participants ≥65 years old were too few to draw conclusions on efficacy. However, in this subpopulation, immunogenicity data are available, see below. In the interim analysis there were 2 cases of COVID-19 in 660 participants. In the updated analysis, there were 12 cases in 1,383 participants (4 for Vaxzevria vs 8 for control; VE = 51.9% [95% CI: -60.0, 85.5]). The majority of participants ≥65 years old received their doses with an interval shorter than 6 weeks.

The level of protection gained from a single dose of Vaxzevria was assessed in an exploratory analysis that included participants who had received one dose. 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, VE from

22 days post-dose 1 was 73.0% (95% CI: 48.8; 85.8 [Vaxzevria 12/7,998 vs control 44/7,982]). In the updated analysis, this was 69.2% (95% CI: 48.5; 82.4 [Vaxzevria 20/11,044 vs control 65/11,015]).

Exploratory analyses showed that increased immunogenicity was associated with a longer dose interval (see *Immunogenicity* Table 5). Efficacy results from subgroup analyses using the updated dataset were consistent with the immunogenicity data (Table 3).

Table 3 Vaxzevria efficacy by dosing interval[a]

Dosing interval	Vaxzevria		Control		Vaccine efficacy % (95% CI)
	N	Number of COVID-19 cases, n (%)	N	Number of COVID-19 cases, n (%)	
<6 weeks	3,905	35 (0.9)	3,871	76 (2.0)	55.1 (33.0, 69.9)
6-8 weeks	1,124	20 (1.8)	1,023	44 (4.3)	59.7 (31.7, 76.3)
9-11 weeks	1,530	14 (0.9)	1,594	52 (3.3)	72.3 (50.0, 84.6)
≥12 weeks	2,038	15 (0.7)	2,093	76 (3.6)	80.0 (65.2, 88.5)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval; [a] Data from the updated analyses (07 December 2020 data cut off).

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} viral particles per dose corresponding to not less than 2.5×10^{8} infectious units) of Vaxzevria (N=17,662) or saline placebo (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 placebo, respectively) received the second dose ≥26 to ≤36 days after dose 1.

Baseline demographics were well balanced across the Vaxzevria and placebo 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 was made by an adjudication committee. Overall vaccine efficacy and efficacy by key age groups are presented in Table 4.

Table 4 – Vaxzevria efficacy against symptomatic COVID-19 illness in Study D8110C00001

	Vaxzevria			**Placebo**			**Vaccine efficacy % (95% CI)[b]**
	N	**Number of COVID-19 cases[a], n (%)**	**Incidence rate of COVID-19 per 1,000 person-years**	**N**	**Number of COVID-19 cases[a], n (%)**	**Incidence rate of COVID-19 per 1,000 person-years**	
Overall (age ≥18 years old)	17,662	73 (0.4)	35.69	8,550	130 (1.5)	137.23	74.0 (65.3, 80.5)
Age 18 to 64 years old	13,966	68 (0.5)	40.47	6,738	116 (1.7)	148.99	72.8 (63.4, 79.9)
Age ≥65 years old	3,696	5 (0.1)	13.69	1,812	14 (0.8)	82.98	83.5 (54.2, 94.1)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval.

[a] Symptomatic COVID-19 requiring positive Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and at least 1 respiratory sign or symptom, or at least 2 other systemic signs or symptoms, as defined in the protocol.

[b] The confidence intervals were not adjusted for multiplicity.

Severe or critical symptomatic COVID-19 illness was assessed as a key secondary endpoint. Among all subjects in the per protocol set, no cases of severe or critical symptomatic COVID-19 were reported in the vaccine group compared with 8 cases reported in the placebo group. There were 9 hospitalised cases, the 8 cases that were adjudicated as severe or critical symptomatic COVID-19, and one additional case in the vaccine group. The majority of the severe or critical symptomatic COVID-19 cases fulfilled only the oxygen saturation (SpO2) criterion for severe disease (≤ 93% on room air).

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 placebo (N=9,031), respectively.

Participants with one or more comorbidities who received Vaxzevria had an efficacy (≥15 days post-dose 2) 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).

In the 6-month follow-up analysis, updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during the blinded placebo-controlled follow-up (median of 78 days in participants who received Vaxzevria and 71 days in participants who received placebo). Overall vaccine efficacy against symptomatic COVID-19 illness was 67.0% (95% CI: (58.9, 73.5) with 141 (0.8%) cases of COVID-19 reported in participants who had received two doses of Vaxzevria (N=17,617) and 184 (2.2%) cases reported in participants who had received placebo (N=8,528). In participants aged 18 to 64 years there were 135 (1.0%) cases in the Vaxzevria group (N=13,921) versus 165 (2.5%) cases in the placebo group (N=6,712), corresponding to a vaccine efficacy of 64.8% (95% CI: 55.7, 71.9). In participants ≥ 65 years old vaccine efficacy was 86.3% (95% CI: 65.8, 94.6) with 6 (0.2%) cases in the Vaxzevria group (N=3,696) versus 19 (1.1%) cases in the placebo group (N=1,816).

The prevention of SARS-CoV-2 infection (symptomatic and asymptomatic) was evaluated by the occurrence of SARS-CoV-2 nucleocapsid antibodies ≥15 days post second dose. In the 6-month follow-up analysis, there were 295 (1.7%) SARS-CoV-2 infections in the Vaxzevria group (N=17,617) and 323 (3.8%) infections in the placebo group (N=8,528), corresponding to a vaccine efficacy of 61.0% (95% CI: 54.4, 66.7).

Immunogenicity

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[a, b]

Population	Baseline	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; 9023.1)	(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)

Population	Baseline	28 days after dose 1	28 days after dose 2
	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)
≥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] in seronegative individuals who received two recommended doses of vaccine.

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 (97.3%; N=149) and second dose (100.0%; N=156). The increase in S-binding antibodies 28 days after second dose was lower for participants ≥65 years old (GMT=19,258.5 [N=161, 95% CI: 16,650.4; 22,275.1]) when compared to participants aged 18-64 years (GMT=32,337.1 [N=1,350, 95% CI: 30,720.8; 34,038.4]). The majority of participants ≥65 years old had a dose interval of <6 weeks, which may have contributed to the lower titres observed.

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- enzyme-linked immunospot (ELISpot) assay were induced after a first dose of Vaxzevria. These did not rise further after a second dose.

Immunogenicity at 6 months in Study D8110C00001
In participants seronegative at baseline, neutralising and S-binding antibody titres decreased after the peak response achieved following the second dose but remained higher than those measured after the first vaccine dose (Table 6). The rate of seroresponse (≥ 4-fold increase from baseline) by S-binding antibodies remained at > 97% over baseline. For neutralising antibodies, it was 41.1% at 28 days after the first dose, increased to 84.7% at 28 days after the second dose and decreased to 52.5% by Day 180.

Table 6 SARS-CoV-2 S-binding and neutralising antibody titres (subjects seronegative at baseline)

Day post dose 1	S-binding antibody titre	Neutralising antibody titre
	GMT (95% CI)	GMT (95% CI)
Day 29	(N=1,398) 5,670.9 (5,289.9; 6,079.3)	(N=1,203) 64.9 (60.0; 70.2)
Day 57	(N=1,669) 19,192.9 (18,218.3; 20,219.7)	(N=1,433) 250.0 (234.2; 266.9)
Day 180	(N=338)	(N=289)

Day post dose 1	S-binding antibody titre	Neutralising antibody titre
	GMT (95% CI)	**GMT (95% CI)**
	9,695.0 (8,108.1; 11,592.6)	117.9 (94.1; 147.7)

Immunogenicity after a booster dose (third dose)

D7220C00001 is a phase II/III partially double-blind, active-controlled study in which 367 participants ≥30 years old previously vaccinated with Vaxzevria 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 all of whom were seronegative at baseline.

The effectiveness of 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 7).

Table 7 Neutralising antibody titres against the ancestral strain following booster dosing with Vaxzevria in participants previously vaccinated with Vaxzevria

	28 days after primary vaccination[a]	**28 days after booster dose**	**GMT ratio[b]**	**Met non-inferiority objective (Y/N)**
n	508	327		
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

Conditional Approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. New information on this medicinal product will be reviewed at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

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.

Genotoxicity/Carcinogenicity
Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine are not expected to have genotoxic potential.

Reproductive toxicity
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 fetuses and pups, indicating placental and lactational transfer, respectively. No Vaxzevria data are available on vaccine excretion in milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine

L-Histidine hydrochloride monohydrate

Magnesium chloride hexahydrate

Polysorbate 80 (E 433)

Ethanol

Sucrose

Sodium chloride

Disodium edetate dihydrate

Water for injections

6.2 Incompatibilities

This vaccine must not be mixed with other medicinal products or diluted.

6.3 Shelf life

Unopened multidose vial
9 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 (2ºC to 8ºC) 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).

After first use
Use as soon as practically possible and within 6 hours. The vaccine may be stored between 2°C and 25°C during the in-use period.

6.4 Special precautions for storage

Unopened multidose vial

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Keep vials in outer carton to protect from light.

After first use

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

6.5 Nature and contents of container

Multidose vial

10-dose vial

5 ml of suspension in a 10-dose vial (clear type I glass) with a halobutyl rubber stopper and an aluminium overseal with a plastic flip-off cap. Pack sizes of 10 multidose vials.

8-dose vial

4 ml of suspension in an 8-dose vial (clear type I glass) with a halobutyl rubber stopper and an aluminium overseal with a plastic flip-off cap. Pack sizes of 10 multidose vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Handling instructions and administration
This vaccine should be handled by a healthcare professional using aseptic technique to ensure the sterility of each dose. The vaccine does not contain any preservative.

Do not use this vaccine after the expiry date which is stated on the label after EXP.

Unopened multidose vial should be stored in a refrigerator (2°C – 8°C). Do not freeze.

Keep the vials in outer carton in order to protect from light.

Vaxzevria is a colourless to slightly brown, clear to slightly opaque suspension. The vaccine should be inspected visually prior to administration and discarded if particulate matter or differences in the described appearance are observed. Do not shake the vial. Do not dilute the suspension.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

The 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. Individuals who have received the first dose of Vaxzevria should receive the second dose of the same vaccine to complete the vaccination course.

Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection to be administered intramuscularly, preferably in the deltoid muscle of the upper arm. 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.

After first dose withdrawal, use the vial as soon as practically possible and within 6 hours (stored at 2°C to 25°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 using agents with activity against adenovirus.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited
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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/06/2023

10 DATE OF REVISION OF THE TEXT

21/11/2023