COVID-19 Vaccine (ChAdOx1-S [recombinant])

Vaxzevria™
5×10^{10} viral particles
Solution for Injection (IM)

Viral Vaccine

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:

COVID-19 Vaccine (ChAdOx1-S* recombinant) 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.
** Corresponding to not less than 2.5×10^8 infectious units (Inf.U)

This product contains genetically modified organisms (GMOs).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Clear to slightly opaque, colourless to slightly brown, particle free, pH 6.6, solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] is indicated for active immunisation of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19).

4.2 Posology and method of administration

Posology

The COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] complete the vaccination course with COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] (see section 4.4).

A booster dose (third dose) of 0.5 ml may be given to individuals who previously received a 2-dose primary vaccination course with COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria]. The third dose should be administered at least 6 months after completing the primary vaccination course.

A single booster/third dose of the COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] may be administered as a heterologous booster dose at least 6 months following completion of primary vaccination with another authorized COVID-19 vaccine when the potential benefits outweigh any potential risks.

Special populations

Elderly population

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

Paediatric population

The safety and efficacy of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] in children and adolescents (aged <18 years old) have not yet been established. No data are available.

Method of administration

COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 special precautions for use

Hypersensitivity including anaphylaxis

Hypersensitivity reactions including anaphylaxis and angioedema have occurred following administration of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 the previous dose of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria].

Concurrent illness

As with other vaccines, administration of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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, COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 have been reported following vaccination with COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria]. A causal relationship has not been established.

As with other vaccines, the benefits and potential risks of vaccinating individuals with COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] should be considered.

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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] may not protect all vaccine recipients.

Interchangeability

There are no safety, immunogenicity or efficacy data to support interchangeability of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria].

4.5 Interaction with other medicinal products and other forms of interaction

The safety, immunogenicity and efficacy of co-administration of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] with other vaccines have not been evaluated.

4.6 Pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] in pregnant women, or women who became pregnant after receiving the vaccine. The data are insufficient to inform on vaccine-associated risk.

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).

As a precautionary measure, vaccination with COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] is not recommended during pregnancy. Use of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] in pregnant women should be based on an assessment of whether the benefits of vaccination outweigh the potential risks.

Breastfeeding

There are no or limited data from the use of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] in lactating women. A risk to breastfed newborns/infants cannot be excluded.

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

As a precautionary measure, it is preferable to avoid vaccination with COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] when breastfeeding.

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

COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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

Overall summary of the safety profile

The overall safety of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] is based on an analysis of pooled data from four clinical trials (COV001, COV002, COV003, and COV005) 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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] or control. Out of these, 12,282 received at least one dose of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria], with a median duration of follow-up of 4.5 months.

Demographic characteristics were generally similar among participants who received COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] and those who received control. Overall, among the participants who received COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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).

In the COV001 study, the observed reactogenicity in participants who received a booster dose (third dose) following a 2-dose primary vaccination course was consistent with the known reactogenicity profile of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria], and was lower after the third dose compared with after the first dose.

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

Adverse drug reactions

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[a]

MedDRA SOC	**Adverse reaction[b]**	**COVID-19 Vaccine (ChAdOx1 S [recombinant]) (N= 10,317)**	**Control[c] (N= 10,141)**
Blood and lymphatic system disorders	Lymphadenopathy[d]	Uncommon (0.3%)	Uncommon (0.3%)
Nervous system disorders	Headache	Very common (52.7%)	Very common (39.8%)
	Dizziness[d]	Uncommon (0.7%)	Uncommon (0.7%)
	Somnolence[d]	Uncommon (0.5%)	Uncommon (0.3%)
Gastrointestinal disorders	Nausea	Very common (22.2%)	Very common (13.4%)
	Vomiting	Common (1.8%)	Uncommon (0.9%)
	Diarrhoea[d]	Common (1.6%)	Common (1.5%)
	Abdominal pain[d]	Uncommon (0.6%)	Uncommon (0.4%)
Skin and subcutaneous tissue disorders	Hyperhidrosis[d]	Uncommon (0.4%)	Uncommon (0.2%)
	Pruritus[d]	Uncommon (0.3%)	Uncommon (0.3%)
	Rash[d]	Uncommon (0.2%)	Uncommon (0.3%)
	Urticaria[d]	Uncommon (0.1%)	Uncommon (0.1%)
Musculoskeletal and connective tissue disorders	Muscle pain (Myalgia)	Very common (43.9%)	Very common (22.3%)
	Joint pain (Arthralgia)	Very common (26.6%)	Very common (13.0%)
	Pain in extremity[d]	Common (1.3%)	Uncommon (0.8%)

MedDRA SOC	Adverse reaction[b]	COVID-19 Vaccine (ChAdOx1 S [recombinant]) (N= 10,317)	Control[c] (N= 10,141)
General disorders and administration site conditions	**Local**		
	Injection site tenderness	Very common (63.8%)	Very common (40.1%)
	Injection site pain	Very common (54.3%)	Very common (37.5%)
	Injection site warmth	Very common (17.9%)	Very common (15.2%)
	Injection site itch (Injection site pruritus)	Very common (13.1%)	Common (7.8%)
	Injection site swelling	Common (3.4%)	Common (1.6%)
	Injection site redness (Injection site erythema)	Common (3.1%)	Common (1.4%)
	Systemic		
	Fatigue	Very common (53.0%)	Very common (38.6%)
	Malaise	Very common (44.4%)	Very common (21.0%)
	Feverishness[e] (Pyrexia)	Very common (33.5%)	Very common (11.0%)
	Chills	Very common (32.2%)	Common (8.4%)
	Fever[e] (Pyrexia)	Common (7.6%)	Common (1.5%)
	Influenza-like illness[d]	Common (1.1%)	Uncommon (0.7%)

[a] Frequencies of ADRs are reported from the safety analysis set where participants received the recommended dose (5×10^{10} vp) as their first dose.

[b] Solicited event reporting terms, where applicable MedDRA preferred terms are given in parentheses

[c] Control was either meningococcal vaccine or saline solution

[d] Unsolicited adverse reaction

[e] Defined as: Feverishness, (subjective) a self-reported feeling of having a fever; Fever, (objective) ≥38°C/100.4°F

Summary of safety data from D8110C00001

Additional safety of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] was established in a randomised 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 received at least one dose, including 21,587 in the COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] group and 10,792 in the placebo group.

Demographic characteristics were generally similar among participants who received COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] and those who received placebo. Overall, among the participants who received COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] 77.6% were 18 to 64 years and 22.4% were ≥65 years of age. Seventy-nine percent of the participants were White, 8.3% were Black, 4.4% were Asian, 4.0% were American Indian or Alaska Native, 0.3% were Native Hawaiian or Other Pacific Islander, 2.4% were of multiple races and 1.7% were not reported or unknown; 44.4% were female and 55.6% male.

The safety profile observed in this Phase III study was consistent with pooled analysis of data from the United Kingdom, Brazil and South Africa (COV001, COV002, COV003, and COV005). Adverse reactions seen in this Phase III trial were observed at similar frequencies as seen in the pooled analysis except the following: feverishness (pyrexia) (0.7%), arthralgia (1.1%), injection site warmth (<0.1%) and injection site pruritus (0.2%). These adverse reactions were solicited adverse events in the

COV001, COV002, COV003, and COV005 studies whereas the D8110C00001 study did not include these as solicited symptoms to report.

Summary of post-authorization data

The following adverse reactions were not observed during clinical trials and have been spontaneously reported during worldwide post-authorisation use of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria].

Immune system disorders: Anaphylactic reaction (frequency: not known)

Skin and subcutaneous tissue disorders: Angioedema (frequency: not known)

Vascular disorders: 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).

Blood and lymphatic system disorders: Thrombocytopenia (frequency: very rare). The majority of reported events occurred in individuals aged 18-59 years old.

Reporting of suspected adverse reactions

For suspected adverse events following immunization, please report to the Food and Drug Administration (FDA) at www.fda.gov.ph.

Adverse events of concern in association with COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] can also be reported to AstraZeneca via www.azcovid-19.com, or at https://contactazmedical.astrazeneca.com/.

The patient should seek medical attention immediately at the first sign of any adverse events following immunization.

4.9 Overdose

Experience of overdose is limited.

There is no specific treatment for an overdose with COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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

Mechanism of action

COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 neutralizing antibody and cellular immune responses.

Clinical efficacy

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

COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] has been evaluated based on pooled data from four on-going randomised, blinded, controlled trials: a Phase I/II Study, COV001 (NCT04324606), in healthy adults 18 to 55 years of age in the UK; a Phase II/III Study, COV002 (NCT04400838), in adults ≥18 years of age (including the elderly) in the UK; a Phase III Study, COV003 (ISRCTN89951424), in adults ≥18 years of age (including the elderly) in Brazil; and a Phase I/II study, COV005 (NCT04444674), 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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] (N=8,597) or control (meningococcal vaccine or saline) (N=8,581). Participants randomised to COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] and control treatment groups. In the pooled analysis, among the participants who received COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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, 10.1% were Black and 3.7% were Asian. 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. COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] significantly decreased the incidence of COVID-19 compared to control (see Table 2).

Table 2 – COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] efficacy against COVID-19 in COV001, COV002, COV003 and COV005[a]

Population	COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 [COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] 18/9,335 vs control 63/9,312]).

Exploratory analyses showed that increased vaccine efficacy was observed with increasing dose interval, see Table 3.

Table 3 – COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] efficacy by dosing interval in COV001, COV002, COV003 and COV005[a]

Dosing interval	COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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

COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] reduced COVID-19 hospitalisation (WHO severity grading ≥4).

In participants who had received two doses of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] (N=945) compared to 13 for control (N=896), with 0 vs 2 cases in the COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] and control groups, respectively, leading to hospitalisation (WHO severity grading ≥4).

Analysis of efficacy data from D8110C00001

COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] has been evaluated based on an analysis from a randomised, double blinded, placebo-controlled Phase III trial conducted in the United States, Peru and Chile. The trial randomised 32,451 healthy adults or those with medically-stable chronic diseases ≥18 years of age. 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. All participants are planned to be followed for up to 1 year for assessments of efficacy against COVID-19 disease.

In the updated primary efficacy analysis 26,212 participants received two doses of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] (N=17,662) or placebo (N=8,550). Participants randomised to COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] received (5×10^{10} vp per dose) 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 received the second dose ≥26 to ≤36 days (95.7% and 95.3%, respectively) after dose 1.

Baseline demographics were balanced across the COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] and the placebo groups. Of the participants who received COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria], 79.1% were aged 18 to 64 years and 20.9% were ≥65 years of age; 43.8% of subjects were female. Of those randomized, 79.3% were White, 7.9% were Black, 4.2%

were Asian, 4.2% were American Indian or Alaska Native, 0.3% were Native Hawaiian or Other Pacific Islander, and 2.4% were of multiple races (1.7% were unknown or not reported). A total of 10,376 (58.8%) participants who received COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] versus 5,105 (59.7%) who received placebo had at least one pre-existing comorbidity. At the time of analysis the median follow up time post dose 2 was 61 days.

Comorbidity was defined as a chronic kidney disease, chronic obstructive pulmonary disease (COPD), lower immune health because of a solid organ transplant, history of obesity (BMI>30), serious heart conditions, sickle cell disease, type 1 and 2 diabetes, asthma, dementia, cerebrovascular diseases, cystic fibrosis, high blood pressure, liver disease, scarring in the lungs (pulmonary fibrosis), thalassemia, history of smoking.

Final determination of COVID-19 cases was made by an adjudication committee. A total of 203 participants had SARS-CoV-2 virologically confirmed COVID-19 occurring ≥15 days post second dose and met either the Category A or Category B criteria, and had no prior evidence of a previous SARS-CoV-2 infection.

Category A: One or more of the following:

- Pneumonia diagnosed by chest x-ray, or computed tomography 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

Category B: Two or more of the following:

- Fever >100°F (>37.8°C) or feverishness
- New or worsening cough
- Myalgia/muscle pain
- Fatigue that interferes with activities of daily living
- Vomiting and/or diarrhoea (only one finding to be counted toward endpoint definition)
- Anosmia and/or ageusia (only one finding to be counted toward endpoint definition)

COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] significantly decreased the incidence of COVID 19 compared to placebo (see Table 4).

Table 4 – COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] efficacy against COVID-19[a]

	COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria]		Placebo		Vaccine efficacy % (95% CI)
	N	Number of COVID-19 cases[b], n (%)	N	Number of COVID-19 cases[b], n (%)	
Updated Primary Efficacy Analysis[c]					
Symptomatic Illness	17,662	73 (0.4)	8,550	130 (1.5)	73.98 (65.34, 80.47)
Key Secondary Efficacy Analyses					
Symptomatic Illness Regardless of Evidence of Prior COVID-19 Infection	18,563	76 (0.4)	9,031	135 (1.5)	73.68 (65.13, 80.13)
Severe or Critical Symptomatic COVID-19[d]	17,662	0 (0.0)	8,550	8 (<0.1)	100.0 (71.62, NE)[e]
COVID-19 Emergency Department Visits	17,662	1 (<0.1)	8,550	9 (0.1)	94.80 (58.98, 99.34)
Post-treatment response for SARS-CoV-2 Nucleocapsid antibodies[f]	17,662	156 (0.9)	8,550	202 (2.4)	64.32 (56.05, 71.03)

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

[a] Based on confirmed COVID-19 cases in subjects aged 18 years and over who were seronegative at baseline, who had received two doses and were on-study ≥15 days post second dose.

[b] Virologically confirmed SARS-CoV-2 using the Category A and B criteria.

[c] Updated primary analysis included all outstanding adjudicated events.

[d] 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.

[e] 97.5%CI

[f] Negative at baseline to positive post treatment with study intervention.

In the pre-specified primary efficacy analysis, based on 190 adjudicated cases, there were 65 (0.4%) COVID-19 cases in participants receiving COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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].

When cumulative incidence of viral shedding was examined with cases occurring ≥15 days post-dose 2, time to clearance of SARS-CoV-2 in saliva samples in COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] participants was notably shorter (11 vs 16 days).

Efficacy in subgroups

Participants with one or more comorbidities who received the COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] ≥15 days post dose-2 had an efficacy of 75.24% (64.18, 82.88) and participants without comorbidities had a vaccine efficacy of 71.81% (95% CI: 55.5, 82.14).

In participants ≥65 years old who had received COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] (≥15 days post-dose 2 N=3,696), there were 5 (0.1%) cases of COVID-19 compared to 14 (0.8%) cases for placebo (N=1,812), corresponding to a vaccine efficacy of 83.5% [95% CI: 54.17, 94.06].

Immunogenicity

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

Following vaccination with COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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; 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)
≥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 4).

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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] with cells expressing IFN-γ, IL-2, and/or TNFα which are generally similar between age categories.

Immunogenicity data in individuals receiving a booster dose (third dose)

COV001 included 90 participants aged 18-55 years who received a booster dose with COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria]. Antibody responses were assessed in 75 participants who had received their two doses of the primary vaccination course within an 8-16 week interval, followed by a booster dose administered between 28 38 weeks after the second dose. Spike IgG antibody titres after the booster dose were significantly higher than after the second dose (median total IgG titre was 1792 EUs [IQR 899–4634] at 28 days after the second dose vs 3746 EUs [2047–6420] 28 days after the booster dose; pairwise comparison in 73 participants for whom samples were available using Wilcoxon signed rank test; p=0.0043).

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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] related inflammation.

Mutagenicity and carcinogenicity

COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] to the gonads (testes, ovaries) following IM injection.

In a reproductive and development toxicity study, COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 (EDTA)
Water for injection

(The names of inactive ingredients may vary according to geographical region)

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

(Please refer to the locally approved shelf-life)

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 (86°F)
- 72 hours down to -3°C (27°F)

Unopened vials must always be returned to refrigerated storage (2 to 8ºC [36 to 46°F]) 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

After first opening, chemical and physical in-use stability has been demonstrated from the time of vial puncture to administration for no more than:

- 6 hours at room temperature, up to 30ºC [86°F], or
- 48 hours in a refrigerator (2 to 8ºC [36 to 46°F]).

The vial can be re-refrigerated, but the cumulative storage time at room temperature must not exceed 6 hours, and the total cumulative storage time must not exceed 48 hours.

6.4 Special precautions for storage

Unopened multidose vial

Store in a refrigerator (2 to 8°C [36 to 46°F]).

Do not freeze.

Store in outer carton in order 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.
- 4 ml of solution in an 8-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 Instructions for use, handling and disposal

Administration

COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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.

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 opening, use the vial within:

- 6 hours when stored at room temperature (up to 30ºC [86°F]), or
- 48 hours when stored in a refrigerator (2 to 8ºC [36 to 46°F]).

The vial can be re-refrigerated, but the cumulative storage time at room temperature must not exceed 6 hours, and the total cumulative storage time must not exceed 48 hours. After this time, the vial must be discarded.

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

COVID-19 Vaccine (ChAdOx1-S [recombinant]) [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 EMERGENCY USE AUTHORIZATION (EUA) HOLDER

AstraZeneca Pharmaceuticals (Phils.), Inc.

8 REGISTRATION NUMBER

Not applicable.

9 DATE OF FIRST AUTHORISATION

Emergency Use Authorization granted on 28 January 2021 for COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] manufactured at Catalent Anagni S.R.L. – Italy.

Emergency Use Authorization granted on 05 May 2021 for COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] manufactured at Siam Bioscience Co., Ltd. – Thailand.

Emergency Use Authorization granted on 10 September 2021 for COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Vaxzevria] manufactured at SK Bioscience Co. Ltd. – Republic of Korea.

10 DATE OF REVISION OF THE TEXT

November 2021
Philippine-specific Text ANGEL Reference: Doc ID-004657059 v3.0

Based on CDS dated 02 November 2021 ANGEL Reference: Doc ID-004450132 v10.0 and FDA Philippines Supplemental Authorization dated 15 November 2021 ANGEL Reference: Doc ID-004725110 v1.0

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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