NEW ZEALAND DATA SHEET

1. PRODUCT NAME

VAXZEVRIA; 5 x 10^{10} viral particles in 0.5 mL solution for injection (previously COVID-19 Vaccine AstraZeneca).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each multidose vial contains 10 doses of 0.5 mL

One dose (0.5 mL) contains 5 x 10^{10} viral particles (vp) of ChAdOx1-S[a, b, c]

[a] Recombinant, replication-deficient chimpanzee adenovirus encoding the SARS-CoV-2 Spike (S) glycoprotein (GP).

[b] The vaccine is manufactured using material originally sourced from a human embryo (Human Embryonic kidney cells HEK293.

[C] Corresponding to not less than 2.5 × 10^{8} infectious units (Inf.U)

This product contains genetically modified organisms (GMOs) under GMO regulations in other jurisdictions. Please note that under the Hazardous Substances and New Organisms (HSNO) Act 1996, this product is not considered to be an organism, and is therefore is not considered a GMO in New Zealand.

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

Solution for injection

Clear to slightly opaque colourless to slightly brown, particle free solution with a pH of 6.1 – 7.1.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VAXZEVRIA has provisional consent (see section 5.1) for the indication below:

Active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Posology

The VAXZEVRIA 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 vaccination course with VAXZEVRIA (see section 4.4).

Special patient populations

Use in the elderly

No dosage adjustment is required in elderly individuals ≥65 years of age (see section 4.4).

Use in paediatric patients

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.

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

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.

Using an aseptic technique, 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 30°C), or
- 48 hours when stored in a refrigerator (2 to 8°C).

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.

There is limited information available in relation to the storage of the vaccine in syringes. For practical reasons, if the contents of the vial are to be used within a short period of time, drawing up the content in multiple syringes at once may be considered. Vaccine in syringes may be kept for up to 6 hours when stored at room temperature (up to 30˚C). However, ensure that the cumulative storage time at room temperature from the first vial puncture to last dose administration does not exceed 6 hours. After this time, the syringe must be discarded.

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.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with any vaccine, vaccination with VAXZEVRIA may not protect all vaccine recipients. Vaccination does not mitigate the need to follow other official recommendations to prevent the spread of COVID-19.

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.

A second dose of the vaccine should not be given to those who have experienced a severe hypersensitivity reaction to the first 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.

Thrombosis 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-marketing 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 but have also been reported after this period. 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 thrombosis 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.

Since medical management of a post-vaccine thrombosis with thrombocytopenia may be different from medical management of other thromboses, if a patient presents with thrombosis and/or thrombocytopenia after receiving a vaccine, healthcare professionals should consult applicable guidance and seek advice from a specialist haematologist 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.

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 these 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 support therapy is usually warranted. Individuals with a known history of CLS should not be vaccinated with this vaccine (see Section 4.3).

Neurological events

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

Immunocompromised individuals

The immunogenicity, efficacy and safety of VAXZEVRIA has not been assessed in immunocompromised individuals, including those receiving immunosuppressive therapy. The immunogenicity of vaccines may be lower in immunosuppressed patients.

Duration and level of protection

The duration of protection has not yet been established. Studies are ongoing.

Interchangeability

There are no safety, immunogenicity or efficacy data to support interchangeability of VAXZEVRIA with other COVID-19 vaccines.

Use in the elderly

There are currently limited data available for the efficacy and safety in individuals over 65 years of age. Further information will be collected from ongoing clinical studies and post-market monitoring. The decision to immunise an elderly patient should be decided on a case-by-case basis with consideration of age, co-morbidities, their environment, potential benefits and potential risks.

Use in individuals with significant co-morbidities

There are currently limited data available for the efficacy and safety in individuals with significant co-morbidities. The decision to immunise an individual should be made on the basis of potential benefits over risks to that individual.

Paediatric use

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

Effects on laboratory tests

Vaccination with VAXZEVRIA leads to the development of antibodies to the SARS-CoV-2 S protein. This does not interfere with results from SARS-CoV-2 PCR testing.

4.5 INTERACTION WITH OTHER MEDICINES 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

There are a limited amount of data from the use of 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 VAXZEVRIA is not recommended during pregnancy. Use of VAXZEVRIA in pregnant women should be based on an assessment of whether the benefits of vaccination outweigh the potential risks.

Breast-feeding

There are no or limited data from the use of VAXZEVRIA in lactating women. A risk to breastfed newborns/infants cannot be excluded.

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

The overall safety of VAXZEVRIA is based on 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 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).

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

Safety in subgroups including the frail elderly, immunosuppressed, and pregnancy is unknown due to the low number of representative participants from these groups. Further information will become available from ongoing clinical studies and pharmacovigilance programmes.

Tabulated list of adverse events

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]	VAXZEVRIA (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%)
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%)

MedDRA SOC	Adverse reaction[b]	VAXZEVRIA (N= 10,317)	Control[c] (N= 10,141)
	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 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 VAXZEVRIA group and 10,792 in the placebo group.

Demographic characteristics were generally similar among participants who received VAXZEVRIA and those who received placebo. Overall, among the participants who received 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.

Post-marketing experience

The following adverse reactions were not observed during clinical trials and have been spontaneously reported during worldwide post-authorisation use of VAXZEVRIA.

Immune system disorders: *Anaphylactic reaction

Skin and subcutaneous tissue disorders: *Angioedema

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.

** The frequency of these adverse reactions is 'not known' (cannot be estimated from available data as the reports come from a population of unknown size).*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/.

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

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 neutralizing antibody and cellular immune responses.

Clinical Efficacy and Safety

<u>Primary analysis of pooled data from COV001, COV002, COV003, and COV005</u>

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. In studies COV001 and COV002, licensed seasonal influenza and pneumococcal vaccinations were permitted (at least 7 days before or after their study vaccine). All participants are planned to be followed for up to 12 months, for assessments of safety and efficacy against COVID-19 disease. These studies are ongoing.

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 COVID- 19 Vaccine AstraZeneca 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, 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. VAXZEVRIA significantly decreased the incidence of COVID-19 compared to control (see Table 2).

Table 2 VAXZEVRIA efficacy against COVID-19 in COV001, COV002, COV003 and COV005[a]

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 3.

Table 3 VAXZEVRIA efficacy by dosing interval in COV001, COV002, COV003 and COV005[a]

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).

Analysis of efficacy data from D8110C00001

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 VAXZEVRIA (N=17,662) or placebo (N=8,550). Participants randomised to 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 VAXZEVRIA and the placebo groups. Of the participants who received 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 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).

VAXZEVRIA significantly decreased the incidence of COVID-19 compared to placebo (see Table 4)..

Table 4 – VAXZEVRIA efficacy against COVID-19[a]

	VAXZEVRIA		Placebo		Vaccine efficacy % (95% CI)
	N	Number of COVID-19	N	Number of COVID-19 cases[b], n (%)	

		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 VAXZEVRIA (N=17,817) and 125 (1.5%) COVID-19 cases in participants receiving control (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 dose-2, time to clearance of SARS-CoV-2 in saliva samples in VAXZEVRIA participants was notably shorter (11 vs 16 days).

Efficacy in subgroups

Participants with one or more comorbidities who received the 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 VAXZEVRIA (≥15 days post-dose 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 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	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 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.

This medicine has been given a provisional consent under Section 23 of the Act. This means that further evidence on this medicine is awaited or that there are specific conditions of use. Refer to the consent notice published in the New Zealand Gazette for the specific conditions.

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 (EDTA)
- Water for injection

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 to 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:

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 30°C, or.
- 48 hours in a refrigerator (2 to 8°C).

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).
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

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Any unused vaccine or waste material should be disposed of in accordance with local requirements. Spills should be disinfected with an appropriate antiviral disinfectant.

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.

For VAXZEVRIA enquiries contact 0800 684 432 or visit azcovid-19.com.

9. DATE OF FIRST APPROVAL

29 July 2021

10. DATE OF REVISION OF THE TEXT

4 April 2022

Doc ID-004633304 v5.0

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Neurological events section is updated to include demyelinating disorders