SUMMARY OF PRODUCT CHARACTERISTICS

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant)

COVISHIELD™

1 NAME OF THE MEDICINAL PRODUCT

COVISHIELD™
ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) 5×10^{10} virus particles (vp)

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

This product contains genetically modified organisms (GMOs).

For the full list of excipients, see section 6.1.

Both **COVISHIELD™** (manufactured by Serum Institute of India Pvt Ltd) and COVID-19 Vaccine AstraZeneca (manufactured by AstraZeneca) are ChAdOx1 nCoV- 19 Corona Virus Vaccines (Recombinant).

3 PHARMACEUTICAL FORM

Solution for injection

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

COVISHIELD™ 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

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

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

Special populations

Elderly population

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

Paediatric population

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

Method of administration

COVISHIELD™ 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 should not receive a second dose of ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant).

4.4 Special warnings and special precautions for use

Hypersensitivity including anaphylaxis

Hypersensitivity reactions including anaphylaxis and angioedema have occurred following administration of ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant).

As with all injectable vaccines, 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 ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant).

Concurrent illness

As with other vaccines, administration of **COVISHIELD™** 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.

- Coagulation disorders *Thromboembolism in combination with 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 ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) 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. 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.

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.

- *Cerebrovascular venous and sinus thrombosis without thrombocytopenia*

Events of cerebrovascular venous and sinus thrombosis without thrombocytopenia have been reported very rarely following vaccination with ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant), 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.

- *Thrombocytopenia*

Cases of thrombocytopenia, including immune thrombocytopenia (ITP), have been reported following vaccination with ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant), 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. Some of these cases occurred in individuals with a history of immune thrombocytopenia or thrombocytopenia. Cases with fatal outcome have been reported. In individual with a history of a thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before vaccination and platelet monitoring is recommended after vaccination.

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 headache, blurred vision, confusion, seizures, shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain, spontaneous bleeding or unusual skin bruising and or petechia a few days after vaccination.

Individuals diagnosed with thrombocytopenia within 21 days of vaccination with ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant), should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 21 days of vaccination should be evaluated for thrombocytopenia.

Risk of bleeding with intramuscular administration

As with other intramuscular injections, **COVISHIELD™** 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

Guillain-Barré Syndrome (GBS) has been reported very rarely following vaccination with ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant). 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.

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.

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.

Duration and level of protection and limitation of effectiveness

The duration of protection has not yet been established.

Protection starts from approximately 3 weeks after the first dose of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant). Individuals may not be fully protected until 15 days after the second dose is administered.

As with any vaccine, vaccination with **COVISHIELD™** may not protect all vaccine recipients (See section 5.1).

Interchangeability

There are limited safety, immunogenicity and efficacy data to support interchangeability of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) with other COVID-19 vaccines. For

the available data on the use of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) as a booster dose following primary vaccination with another COVID-19 vaccine, see sections 4.8 and 5.1.

4.5 Interaction with other medicinal products and other forms of interaction

The safety, immunogenicity and efficacy of co-administration of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) with other vaccines have not been evaluated.

4.6 Fertility, pregnancy and lactation

Fertility

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

Pregnancy

Data from more than 400 case reports of pregnant women or women who became pregnant after receiving ChAdOx1 nCoV-19 Corona Virus Vaccine do not suggest unusual patterns of pregnancy complications or foetal/neonatal outcomes. No increased risk of maternal thrombosis in combination with thrombocytopenia has been observed.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or post-natal development;
Administration of **COVISHIELD™ in** pregnancy may be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Breastfeeding

Anti-SARS-CoV-2 S antibodies are excreted in breast milk of mothers vaccinated with ChAdOx1 nCoV-19 Corona Virus Vaccine. In animal studies, lactational transfer of anti-SARS-CoV-2 S antibodies from maternal female mice to pups was observed (see section 5.3). It is unknown whether the vaccine itself is excreted in human milk. In animal studies no quantifiable levels of the vaccine were detected in the mammary gland in female mice.

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

4.7 Effects on ability to drive and use machines

ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) 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 from the Overseas studies:

Primary vaccination course

The overall safety of COVID-19 Vaccine AstraZeneca [ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)] 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, in which 24,221 participants ≥18 years old -were randomised and received either COVID-19 Vaccine AstraZeneca or control. Out of these, 12,257 received at least one dose of COVID-19 Vaccine AstraZeneca, with a median duration of placebo-controlled blinded follow- up of 6.3 months.

Participants continued to be followed for safety regardless of unblinding or receipt of unblinded vaccination, and longer follow-up of ≥12 months (median 13.0 months) is available for 10,247 participants.

Demographic characteristics were generally similar among participants who received COVID-19 Vaccine AstraZeneca and those who received control. Overall, among the participants who received COVID-19 Vaccine AstraZeneca, 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).

Booster dose (third dose)

In study D7220C00001, 367 participants who had previously received a 2-dose primary vaccination course with COVID-19 Vaccine AstraZeneca [ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)], and 322 participants who had previously received a 2-dose primary vaccination

course with an mRNA vaccine received a single booster dose (third dose) of COVID-19 Vaccine AstraZeneca. The safety profile observed in participants who received a booster dose (third dose) was consistent with the known safety profile of COVID-19 Vaccine AstraZeneca. The reactogenicity observed in participants who had previously received primary vaccination with an mRNA vaccine was similar to the reactogenicity observed in participants receiving a first dose of COVID-19 Vaccine AstraZeneca in previous clinical studies.

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

In the externally sponsored study RHH-001, 304 participants received a single booster dose (third dose) of COVID-19 Vaccine AstraZeneca following a 2-dose primary vaccination course with an inactivated whole-virion SARS-CoV-2 vaccine. The reported reactogenicity profile was consistent with the known reactogenicity profile of COVID-19 Vaccine AstraZeneca.

No new safety concerns, as compared with adverse reactions reported for the primary vaccination course with COVID-19 Vaccine AstraZeneca, have been identified in individuals receiving a booster dose of COVID-19 Vaccine AstraZeneca.

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.

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] based on an analysis of pooled data from COV001, COV002, COV003, and COV005

MedDRA SOC	**Adverse reaction[b]**	**Vaxzevria (N= 10,304)**	**Control[c] (N= 10,141)**
Blood and lymphatic system disorders	Lymphadenopathy[d]	Uncommon (0.4%)	Uncommon (0.5%)

Metabolism and nutrition disorders	Decreased appetite	Uncommon (0.6%)	Uncommon (0.2%)
Nervous system disorders	Headache	Very common (52.-6%)	Very common (-40.4%)
	Dizziness[d]	Common (- 1.0 %)	Uncommon (0.9%)
	Somnolence[d]	Uncommon (0.5%)	Uncommon (0.4%)
Gastrointestinal disorders	Nausea	Very common (22.2%)	Very common (13.9%)
	Diarrhoea[d]	Common (2.6%)	Common (2.3%)
	Vomiting	Common (1.7%)	Common (1.0%)
	Abdominal pain[d]	Common (1.0%)	Uncommon (0.8%)
Skin and subcutaneous tissue disorders	Hyperhidrosis[d]	Uncommon (0.5%)	Uncommon (0.2%)
	Pruritus[d]	Uncommon (0.4%)	Uncommon (0.4%)
	Rash[d]	Uncommon (0.4%)	Uncommon (0.4%)
	Urticaria[d]	Uncommon (0.1%)	Rare (≤0.1%)
Musculoskeletal and connective tissue disorders	Muscle pain (Myalgia)	Very common (43.8%)	Very common (23.1%)
	Joint pain (Arthralgia)	Very common (26.4%)	Very common (13.4%)
	Pain in extremity[d]	Common (15%)	Common (1.1%)
General disorders and administration site conditions	**Local**		
	Injection site tenderness	Very common (63.6%)	Very common (40.5%)
	Injection site pain	Very common (54.9%)	Very common (38.4%)
	Injection site warmth	Very common (18.4%)	Very common (15.6%)
	Injection site itch (Injection site pruritus)	Very common (13.2%)	Common (8.1%)
	Injection site swelling	Common (-3.5%)	Common (1.6%)
	Injection site redness (Injection site erythema)	Common (3.1%)	Common (1.4%)
	Systemic		
	Fatigue	Very common (53.2%)	Very common (39.1 %)

	Malaise	Very common (44.3%)	Very common (21.8%)
	Feverishness[e] (Pyrexia)	Very common (33.4%)	Very common (12.1%)
	Chills	Very common (31.9%)	Common (9.2%)
	Fever[e] (Pyrexia)	Common (7.8%)	Common (1.4%)
	Influenza-like illness[d]	Common (1.1%)	Uncommon (0.8%)

[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 (Phase 3 Study in US, Peru and Chile):

Additional safety of COVID-19 Vaccine AstraZeneca 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 AstraZeneca group and 10,792 in the placebo group.

Demographic characteristics were generally similar among participants who received COVID-19 Vaccine AstraZeneca and those who received placebo. Overall, among the participants who received COVID-19 Vaccine AstraZeneca 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 global post-authorisation data of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)

The following adverse reactions were not observed during clinical trials and have been spontaneously reported during worldwide post-authorisation use of COVID-19 Vaccine AstraZeneca.

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

Skin and subcutaneous tissue disorders: Angioedema (frequency: not known), cutaneous vasculitis (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.

Immune thrombocytopenia (frequency: not known).

Nervous system disorders: Paraesthesia and hypoaesthesia (frequency: uncommon). Many of these events were co-reported with reactogenicity events.

Facial paralysis (frequency: rare), Guillain-Barré syndrome (frequency: very rare)

Ear and labyrinth disorders: Tinnitus (frequency: uncommon).

Overall summary of the safety profile from the Indian study:

COVISHIELD™ was also safe and well tolerated in the phase 2/3 clinical trial in India. This study included data of all 1600 participants who received first dose [1200 in **COVISHIELD™** group, 100 in COVID-19 Vaccine AstraZeneca group and 300 in Placebo group]. This final analysis includes data collected until Day 180 visit of all 1600 participants who received first dose and 1577 participants who received second dose.

Demographic characteristics were generally similar among participants across the three groups. Overall, among the participants who received COVISHIELD™, 87.3% were aged 18 to 59 years and 12.7% were 60 years of age or older.

Overall, the incidence of solicited reactions (injection site reactions: pain, tenderness, redness, warmth, itch, swelling and induration; and systemic reactions: fever, chills, fatigue, malaise, headache, arthralgia and myalgia), unsolicited adverse events and serious adverse events (SAEs) was comparable in the study and control groups.

A total of 27 (1.7%) participants reported 27 SAEs, 21 (1.8%) in COVISHIELD™ group, (1.3%) in placebo group and 2 (2·0%) in COVID-19 Vaccine AstraZeneca group. **None of these SAEs were assessed as related to study vaccine. There were no thromboembolic-associated or autoimmune-related SAEs** reported in the study**.**

Table 2 – Adverse drug reactions from COVISHIELD™ study in India

MedDRA SOC	Frequency	Adverse reactions
Gastrointestinal disorders	Common	Nausea
	Uncommon	Diarrhoea
General disorders and administration site conditions	Very common	Injection site pain
	Common	Pyrexia, malaise, fatigue, pain, chills, injection site erythema, injection site swelling, injection site induration, asthenia, injection site pruritus
Musculoskeletal and connective tissue disorders	Common	Myalgia, arthralgia
	Uncommon	Pain in extremity, back pain, neck pain
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, somnolence
Skin and subcutaneous tissue disorders	Uncommon	Urticaria

Summary of post-authorisation data in India

The following adverse reactions were not observed during clinical trials and have been spontaneously reported during post-authorisation use of COVISHIELD™ in India.

Immune system disorders: Anaphylactic reaction (frequency: very rare), Hypersensitivity reactions (frequency: very rare)

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 1/79,830,000. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia (see section 4.4).

Blood and lymphatic system disorders: Thrombocytopenia (frequency: very rare).

Immune thrombocytopenia (frequency: very rare).

Nervous system disorders: Paraesthesia and hypoaesthesia (frequency: very rare).

Facial paralysis (frequency: very rare), Guillain-Barré syndrome (frequency: very rare/ unknown)

Ear and labyrinth disorders: Tinnitus (frequency: very rare).

Skin and subcutaneous tissue disorders: Angioedema (frequency: very rare), cutaneous vasculitis (frequency: very rare).

4.9 Overdose

Experience of overdose is limited.

There is no specific treatment for an overdose with ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant). In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

COVISHIELD™ 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.

Efficacy and immunogenicity data from the Overseas studies:

Clinical efficacy

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

COVID-19 Vaccine AstraZeneca [ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)] has been evaluated based on pooled data from four on-going randomised, blinded, controlled studies: 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 history of anaphylaxis or angioedema; 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). 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 primary analysis for efficacy, participants ≥18 years of age received two doses of COVID-19 Vaccine AstraZeneca (N=8,597) or control (meningococcal vaccine or saline) (N=8,581). Participants randomised to COVID-19 Vaccine AstraZeneca 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 primary analysis, among the participants who received COVID-19 Vaccine AstraZeneca, 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 3056 (35.5%) participants had at least one pre-existing comorbidity (defined as a BMI ≥ 30 kg/m2, 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 143 days and 83 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 332 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. COVID-19 Vaccine AstraZeneca significantly decreased the incidence of COVID-19 compared to control (see Table 2a).

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

Population	COVID-19 Vaccine AstraZeneca		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)	8597	84 (0.98)	8581	248 (2.89)	66.73 (57.41, 74.01)
Licensing regimen					
SDSD	7201	74 (1.03)	7179	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 AstraZeneca 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 AstraZeneca 18/9,335 vs control 63/9,312]).

Exploratory analyses showed that increased vaccine efficacy was observed with increasing dose interval, see Table 2b.

Table 2b - COVID-19 Vaccine AstraZeneca efficacy by dosing interval in COV001, COV002, COV003 and COV005[a]

Dosing interval	COVID-19 Vaccine AstraZeneca		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 (33.0, 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.
[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 AstraZeneca reduced COVID-19 hospitalisation (WHO severity grading ≥4).

In participants who had received two doses of COVID-19 Vaccine AstraZeneca (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).

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 AstraZeneca (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 AstraZeneca (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 AstraZeneca (N=945) compared to 13 for control (N=896), with 0 vs 2 cases in the COVID-19 Vaccine AstraZeneca and control groups, respectively, leading to hospitalisation (WHO severity grading ≥4).

Analysis of efficacy data from D8110C00001

COVID-19 Vaccine AstraZeneca 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 AstraZeneca (N=17,662) or placebo (N=8,550). Participants randomised to COVID-19 Vaccine AstraZeneca 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 AstraZeneca and the placebo groups. Of the participants who received COVID-19 Vaccine AstraZeneca, 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 AstraZeneca 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 AstraZeneca significantly decreased the incidence of COVID-19 compared to placebo (see Table 3).

Table 3 – COVID-19 Vaccine AstraZeneca efficacy against COVID-19[a]

	COVID-19 Vaccine AstraZeneca		Placebo		
	N	Number of COVID-19 cases[b], n (%)	N	Number of COVID-19 cases[b], n (%)	Vaccine efficacy % (95% CI)
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	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	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 AstraZeneca (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 AstraZeneca participants was notably shorter (11 vs 16 days).

Efficacy in subgroups

Participants with one or more comorbidities who received the COVID-19 Vaccine AstraZeneca ≥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 AstraZeneca (≥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].

Updated efficacy analyses

In the 6-month follow-up analysis, updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, with a median follow-up time post second dose of 78 days in participants who received COVID-19 Vaccine AstraZeneca and 71 days in participants who received placebo. Overall vaccine efficacy against

symptomatic COVID-19 illness was 66.98% (95% CI: 58.87, 73.50) with 141 (0.80%) cases of COVID-19 reported in participants who had received two doses of COVID-19 Vaccine AstraZeneca (N=17,617) and 184 (2.16%) cases reported in participants who had received placebo (N=8,528). In participants ≥65 years old there were 6 (0.16%) cases reported in the COVID-19 Vaccine AstraZeneca group (N=3,696) compared with 19 (1.05%) cases in the placebo group (N=1,816), corresponding to a vaccine efficacy of 86.35% (95% CI: 65.79, 94.55).

In individuals with or without prior evidence of SARS-CoV-2 infection, vaccine efficacy against symptomatic COVID-19 illness was 66.96% (95% CI: 58.94, 73.41) with 144 (0.78%) versus 189 (2.11%) cases of COVID-19 in the COVID-19 Vaccine AstraZeneca (N=18,450) and placebo (N=8,960) groups, respectively.

Against severe or critical symptomatic COVID-19 illness, vaccine efficacy was 95.69% (95% CI: 66.33, 99.45) with 1 (0.01%) case reported in the COVID-19 Vaccine AstraZeneca group (N=17,617) and 10 (0.12%) cases reported in the placebo group (N=8,528). There were 2 (0.01%) versus 15 (0.18%) cases of COVID-19-related emergency department visits in the COVID-19 Vaccine AstraZeneca (N=17,617) and placebo (N=8,528) groups, respectively, corresponding to a vaccine efficacy of 94.17% (95% CI: 74.49, 98.67).

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 (1.67%) SARS-CoV-2 infections in the COVID-19 Vaccine AstraZeneca group (N=17,617) and 323 (3.79%) infections in the placebo group (N=8,528), corresponding to a vaccine efficacy of 61.01% (95% CI: 54.35; 66.70).

Immunogenicity

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

Following vaccination with COVID-19 Vaccine AstraZeneca, 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 4).

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 4 – SARS CoV-2 S-binding antibody response to COVID-19 Vaccine AstraZeneca[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=1538) 57.1 (53.8, 60.6)	(N=1466) 8358.0 (7879.2, 8866.0)	(N=1511) 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=18759.6 [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 (Table 3). The majority of participants ≥65 years old had a dose interval of <6 weeks, which may have contributed to the numerically 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-ɣ enzyme-linked immunospot (ELISpot) assay are induced after a first dose of COVID-19 Vaccine AstraZeneca. 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 AstraZeneca with cells expressing IFN-γ, IL-2, and/or TNFα which are generally similar between

age categories.

Study D7220C00001, immunogenicity of a booster dose following primary vaccination with COVID-19 Vaccine AstraZeneca *or an mRNA COVID-19 vaccine*

D7220C00001 is a phase II/III partially double-blind, active-controlled study in which 367 participants ≥18 years old previously vaccinated with COVID-19 Vaccine AstraZeneca and 322 participants ≥18 years old previously vaccinated with an mRNA vaccine received a single booster dose of COVID-19 Vaccine AstraZeneca at least 90 days after receiving the second dose of their primary vaccination course. Immunogenicity was assessed in 342 participants previously vaccinated with COVID-19 Vaccine AstraZeneca and 294 participants previously vaccinated with an mRNA vaccine, all of whom were seronegative at baseline. Participants previously vaccinated with COVID-19 Vaccine AstraZeneca were older than participants previously vaccinated with an mRNA vaccine with 45.9% and 26.9% being ≥65 years of age in the two groups, respectively. Approximately 47% of the participants had at least one pre-existing comorbidity (defined as BMI ≥30 kg/m2, significant cardiovascular disease, chronic lung disease, or diabetes).

The effectiveness of COVID-19 Vaccine AstraZeneca administered as a single booster dose in participants previously vaccinated with COVID-19 Vaccine AstraZeneca was demonstrated by evaluating non-inferiority of the immune response of neutralising 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 neutralising antibody titres 28 days after the booster dose to titres 28 days after the primary vaccination course (see Table 5).

Table 5: Neutralising antibody titres against the ancestral strain following booster dosing with COVID-19 Vaccine AstraZeneca in participants previously vaccinated with COVID-19 Vaccine AstraZeneca

	28 days after primary vaccination course with COVID-19 Vaccine AstraZeneca[a]	**28 days after booster dose**	**GMT ratio[b]**	**Met non-inferiority objective (Y/N)**
n	508	327	327/508	
GMT [c]	242.80	248.89	1.03	Y[d]
(95% CI)	(224.82, 262.23)	(229.53, 269.89)	(0.92, 1.15)	

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

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

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

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

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

COVID-19 Vaccine AstraZeneca was also shown to be effective in eliciting antibody responses in

participants who had previously received primary vaccination with an mRNA vaccine. In these participants, a single booster dose of COVID-19 Vaccine AstraZeneca resulted in increased humoral responses, with geometric mean fold rise (GMFR) of 3.77 (95% CI: 3.26, 4.37) in neutralising antibody titres against the ancestral strain from pre-booster to 28 days after the booster dose.

Booster dosing with COVID-19 Vaccine AstraZeneca increased humoral responses also in participants with serological evidence of prior SARS-CoV-2 infection at baseline, and against all analysed variants, i.e. Alpha, Beta, Gamma, Delta and Omicron.

COV001 Immunogenicity of a booster dose (third dose) following primary vaccination with COVID-19 Vaccine AstraZeneca

COV001 included 90 participants aged 18-55 years who received a booster dose with COVID-19 Vaccine AstraZeneca. 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).

RHH-001 immunogenicity of a booster dose (third dose) following primary vaccination with an inactivated whole-virion COVID-19 vaccine

The externally sponsored RHH-001 was a phase IV single-blind, randomised study, in which antibodies were assessed in 296 Brazilian participants >18 years old who received a booster dose of COVID-19 Vaccine AstraZeneca 5-7 months after receiving the second dose of an inactivated whole-virion COVID-19 vaccine.

At 28 days after receipt of a booster dose of COVID-19 Vaccine AstraZeneca there was a substantial increase from baseline in spike IgG antibody titres (Day 28 GMT 335213 [95% CI: 295598, 380136], baseline GMT 3745 [95% CI: 3252, 4313]). The GMFR from baseline to Day 28 was 90 (95%, CI: 77, 104). Participants who had received a booster dose of COVID-19 Vaccine AstraZeneca had spike IgG antibody titres at Day 28 that were statistically superior to those induced by a booster dose of the inactivated whole-virion COVID-19 vaccine. Geometric mean ratio (GMR) for COVID-19 Vaccine AstraZeneca booster dose versus the inactivated COVID-19 vaccine booster dose was 7.0 (95% CI 6.1, 8.1, p<0,0001). Booster dosing with COVID-19 Vaccine AstraZeneca also increased neutralisation antibody titres against the Delta and Omicron variants.

Immunogenicity data from the Indian study:

GMTs of IgG antibodies against spike (S) protein were comparable between the groups at baseline – Day 1. GMTs increased significantly after each dose of vaccine in both the groups

and were comparable. There was > 98% seroconversion in both the groups on Day 57. The immunogenicity data indicates that COVISHIELD™ is comparable in terms of anti-S IgG antibody titers and seroconversion rates to COVID-19 Vaccine AstraZeneca (see Tables 6 and 7).

Table 6 Summary of Anti-S IgG antibodies

Timepoint	Statistic	COVISHIELD™ (N=297) n (%)	COVID-19 Vaccine AstraZeneca (N=98)
Baseline	N	297	98
	GMT	95.4	79.4
	95% CI	(78.1, 116.6)	(58.2, 108.4)
28 days after Dose 1	N	295	98
	GMT	10131.1	6660.8
	95% CI	(8473.2, 12007.9)	(4836.3, 9173.7)
28 days after Dose 2	n	293	95
	GMT	30245.6	28558.3
	95% CI	(26794.0, 34141.8)	(23479.3, 34735.8)
180 days after Dose 1	n	258	88
	GMT	10134.2	15539.2
	95% CI	(8497.4, 12086.4)	(10317.1, 23404.4)

Table 7 Summary of Proportion of Participants with Seroconversion for Anti-S IgG Antibodies

Timepoint	Statistic	COVISHIELD™ (N=297)	COVID-19 Vaccine AstraZeneca (N=98)
28 days after Dose 1	N Evaluated	295	98
	Seroconversion, n (%)	285 (96.6)	90 (91.8)
	95% CI	(93.9, 98.4)	(84.5, 96.4)
28 days after Dose 2	N Evaluated	293	95
	Seroconversion, n (%)	287 (98.0)	94 (98.9)
	95% CI	(95.6, 99.2)	(94.3, 100.0)
180 days after Dose 1	N Evaluated	258	88
	Seroconversion, n (%)	243 (94.2)	85 (96.6)

Timepoint	Statistic	COVISHIELD™ (N=297)	COVID-19 Vaccine AstraZeneca (N=98)
	95% CI	(90.6, 96.7)	(90.4, 99.3)

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 AstraZeneca 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 AstraZeneca related inflammation.

Mutagenicity and carcinogenicity

ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) 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 AstraZeneca to the gonads (testes, ovaries) following IM injection.

In a reproductive and development toxicity study, COVID-19 Vaccine AstraZeneca 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.

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

The expiry date of vaccine is indicated on the label and packaging.

Once opened, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2ºC and +25ºC. All opened multidose vials of **COVISHIELD™** should be discarded at the end of immunization session or within six hours whichever comes first.

6.4 Special precautions for storage

Store in a refrigerator (+2ºC to +8ºC). Do not freeze. Keep vials in outer carton to protect from light. Discard if vaccine has been frozen.

Opened multidose vial (After first use)

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

6.5 Nature and contents of container

COVISHIELD™ is supplied as ready to use liquid in rubber-stoppered multidose vial and single dose vial in below listed presentations

1 dose – 0.5 mL per vial
2 dose – 1.0 mL per vial
5 dose – 2.5 mL per vial
10 dose – 5.0 mL per vial
20 dose – 10 mL per vial

6.6 Instructions for use, handling and disposal

Administration

COVISHIELD™ is a colourless to slightly brown, clear to slightly opaque solution. 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.

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. 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. Aseptic technique should be used for withdrawing the dose for administration.

After first opening, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2ºC and +25ºC. Discard any unused vaccine.

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

Disposal

COVISHIELD™ 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 (e.g. Hydrogen peroxide-based disinfectants).

7 MARKETING AUTHORIZATION

Serum Institute of India Pvt. Ltd.
212/2, Hadapsar, Pune 411028, India.

Marketed by:

SERUM INSTITUTE LIFE SCIENCES PVT. LTD.
401, Sarosh Bhavan, 16-B/1, Dr. Ambedkar Road, Pune - 411 001, INDIA

8 MARKETING AUTHORISATION NUMBER (S)

MF/BIO/21/000001; Dated 27 January 2022

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of First Authorization: 27 January 2022

Trademark under registration

SUMMARY OF PRODUCT CHARACTERISTICS

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant)

COVISHIELD™

1 NAME OF THE MEDICINAL PRODUCT

COVISHIELD™
ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) 5×10^{10} virus particles (vp)

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

This product contains genetically modified organisms (GMOs).

For the full list of excipients, see section 6.1.

Both **COVISHIELD™** (manufactured by Serum Institute of India Pvt Ltd) and COVID-19 Vaccine AstraZeneca (manufactured by AstraZeneca) are ChAdOx1 nCoV- 19 Corona Virus Vaccines (Recombinant).

3 PHARMACEUTICAL FORM

Solution for injection

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

COVISHIELD™ 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

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

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

Special populations

Elderly population

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

Paediatric population

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

Method of administration

COVISHIELD™ 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 should not receive a second dose of ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant).

4.4 Special warnings and special precautions for use

Hypersensitivity including anaphylaxis

Hypersensitivity reactions including anaphylaxis and angioedema have occurred following administration of ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant).

As with all injectable vaccines, 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 ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant).

Concurrent illness

As with other vaccines, administration of **COVISHIELD™** 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.

- Coagulation disorders *Thromboembolism in combination with 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 ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) 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. 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.

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.

- *Cerebrovascular venous and sinus thrombosis without thrombocytopenia*

Events of cerebrovascular venous and sinus thrombosis without thrombocytopenia have been reported very rarely following vaccination with ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant), 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.

- *Thrombocytopenia*

Cases of thrombocytopenia, including immune thrombocytopenia (ITP), have been reported following vaccination with ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant), 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. Some of these cases occurred in individuals with a history of immune thrombocytopenia or thrombocytopenia. Cases with fatal outcome have been reported. In individual with a history of a thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before vaccination and platelet monitoring is recommended after vaccination.

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 headache, blurred vision, confusion, seizures, shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain, spontaneous bleeding or unusual skin bruising and or petechia a few days after vaccination.

Individuals diagnosed with thrombocytopenia within 21 days of vaccination with ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant), should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 21 days of vaccination should be evaluated for thrombocytopenia.

Risk of bleeding with intramuscular administration

As with other intramuscular injections, **COVISHIELD™** 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

Guillain-Barré Syndrome (GBS) has been reported very rarely following vaccination with ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant). 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.

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.

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.

Duration and level of protection and limitation of effectiveness

The duration of protection has not yet been established.

Protection starts from approximately 3 weeks after the first dose of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant). Individuals may not be fully protected until 15 days after the second dose is administered.

As with any vaccine, vaccination with **COVISHIELD™** may not protect all vaccine recipients (See section 5.1).

Interchangeability

There are limited safety, immunogenicity and efficacy data to support interchangeability of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) with other COVID-19 vaccines. For

the available data on the use of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) as a booster dose following primary vaccination with another COVID-19 vaccine, see sections 4.8 and 5.1.

4.5 Interaction with other medicinal products and other forms of interaction

The safety, immunogenicity and efficacy of co-administration of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) with other vaccines have not been evaluated.

4.6 Fertility, pregnancy and lactation

Fertility

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

Pregnancy

Data from more than 400 case reports of pregnant women or women who became pregnant after receiving ChAdOx1 nCoV-19 Corona Virus Vaccine do not suggest unusual patterns of pregnancy complications or foetal/neonatal outcomes. No increased risk of maternal thrombosis in combination with thrombocytopenia has been observed.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or post-natal development;
Administration of **COVISHIELD™ in** pregnancy may be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Breastfeeding

Anti-SARS-CoV-2 S antibodies are excreted in breast milk of mothers vaccinated with ChAdOx1 nCoV-19 Corona Virus Vaccine. In animal studies, lactational transfer of anti-SARS-CoV-2 S antibodies from maternal female mice to pups was observed (see section 5.3). It is unknown whether the vaccine itself is excreted in human milk. In animal studies no quantifiable levels of the vaccine were detected in the mammary gland in female mice.

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

4.7 Effects on ability to drive and use machines

ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) 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 from the Overseas studies:

Primary vaccination course

The overall safety of COVID-19 Vaccine AstraZeneca [ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)] 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, in which 24,221 participants ≥18 years old -were randomised and received either COVID-19 Vaccine AstraZeneca or control. Out of these, 12,257 received at least one dose of COVID-19 Vaccine AstraZeneca, with a median duration of placebo-controlled blinded follow- up of 6.3 months.

Participants continued to be followed for safety regardless of unblinding or receipt of unblinded vaccination, and longer follow-up of ≥12 months (median 13.0 months) is available for 10,247 participants.

Demographic characteristics were generally similar among participants who received COVID-19 Vaccine AstraZeneca and those who received control. Overall, among the participants who received COVID-19 Vaccine AstraZeneca, 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).

Booster dose (third dose)

In study D7220C00001, 367 participants who had previously received a 2-dose primary vaccination course with COVID-19 Vaccine AstraZeneca [ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)], and 322 participants who had previously received a 2-dose primary vaccination

course with an mRNA vaccine received a single booster dose (third dose) of COVID-19 Vaccine AstraZeneca. The safety profile observed in participants who received a booster dose (third dose) was consistent with the known safety profile of COVID-19 Vaccine AstraZeneca. The reactogenicity observed in participants who had previously received primary vaccination with an mRNA vaccine was similar to the reactogenicity observed in participants receiving a first dose of COVID-19 Vaccine AstraZeneca in previous clinical studies.

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

In the externally sponsored study RHH-001, 304 participants received a single booster dose (third dose) of COVID-19 Vaccine AstraZeneca following a 2-dose primary vaccination course with an inactivated whole-virion SARS-CoV-2 vaccine. The reported reactogenicity profile was consistent with the known reactogenicity profile of COVID-19 Vaccine AstraZeneca.

No new safety concerns, as compared with adverse reactions reported for the primary vaccination course with COVID-19 Vaccine AstraZeneca, have been identified in individuals receiving a booster dose of COVID-19 Vaccine AstraZeneca.

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.

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] based on an analysis of pooled data from COV001, COV002, COV003, and COV005

MedDRA SOC	**Adverse reaction[b]**	**Vaxzevria (N= 10,304)**	**Control[c] (N= 10,141)**
Blood and lymphatic system disorders	Lymphadenopathy[d]	Uncommon (0.4%)	Uncommon (0.5%)

Metabolism and nutrition disorders	Decreased appetite	Uncommon (0.6%)	Uncommon (0.2%)
Nervous system disorders	Headache	Very common (52.-6%)	Very common (-40.4%)
	Dizziness[d]	Common (- 1.0 %)	Uncommon (0.9%)
	Somnolence[d]	Uncommon (0.5%)	Uncommon (0.4%)
Gastrointestinal disorders	Nausea	Very common (22.2%)	Very common (13.9%)
	Diarrhoea[d]	Common (2.6%)	Common (2.3%)
	Vomiting	Common (1.7%)	Common (1.0%)
	Abdominal pain[d]	Common (1.0%)	Uncommon (0.8%)
Skin and subcutaneous tissue disorders	Hyperhidrosis[d]	Uncommon (0.5%)	Uncommon (0.2%)
	Pruritus[d]	Uncommon (0.4%)	Uncommon (0.4%)
	Rash[d]	Uncommon (0.4%)	Uncommon (0.4%)
	Urticaria[d]	Uncommon (0.1%)	Rare (≤0.1%)
Musculoskeletal and connective tissue disorders	Muscle pain (Myalgia)	Very common (43.8%)	Very common (23.1%)
	Joint pain (Arthralgia)	Very common (26.4%)	Very common (13.4%)
	Pain in extremity[d]	Common (15%)	Common (1.1%)
General disorders and administration site conditions	**Local**		
	Injection site tenderness	Very common (63.6%)	Very common (40.5%)
	Injection site pain	Very common (54.9%)	Very common (38.4%)
	Injection site warmth	Very common (18.4%)	Very common (15.6%)
	Injection site itch (Injection site pruritus)	Very common (13.2%)	Common (8.1%)
	Injection site swelling	Common (-3.5%)	Common (1.6%)
	Injection site redness (Injection site erythema)	Common (3.1%)	Common (1.4%)
	Systemic		
	Fatigue	Very common (53.2%)	Very common (39.1 %)

	Malaise	Very common (44.3%)	Very common (21.8%)
	Feverishness[e] (Pyrexia)	Very common (33.4%)	Very common (12.1%)
	Chills	Very common (31.9%)	Common (9.2%)
	Fever[e] (Pyrexia)	Common (7.8%)	Common (1.4%)
	Influenza-like illness[d]	Common (1.1%)	Uncommon (0.8%)

[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 (Phase 3 Study in US, Peru and Chile):

Additional safety of COVID-19 Vaccine AstraZeneca 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 AstraZeneca group and 10,792 in the placebo group.

Demographic characteristics were generally similar among participants who received COVID-19 Vaccine AstraZeneca and those who received placebo. Overall, among the participants who received COVID-19 Vaccine AstraZeneca 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 global post-authorisation data of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)

The following adverse reactions were not observed during clinical trials and have been spontaneously reported during worldwide post-authorisation use of COVID-19 Vaccine AstraZeneca.

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

Skin and subcutaneous tissue disorders: Angioedema (frequency: not known), cutaneous vasculitis (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.

Immune thrombocytopenia (frequency: not known).

Nervous system disorders: Paraesthesia and hypoaesthesia (frequency: uncommon). Many of these events were co-reported with reactogenicity events.

Facial paralysis (frequency: rare), Guillain-Barré syndrome (frequency: very rare)

Ear and labyrinth disorders: Tinnitus (frequency: uncommon).

Overall summary of the safety profile from the Indian study:

COVISHIELD™ was also safe and well tolerated in the phase 2/3 clinical trial in India. This study included data of all 1600 participants who received first dose [1200 in **COVISHIELD™** group, 100 in COVID-19 Vaccine AstraZeneca group and 300 in Placebo group]. This final analysis includes data collected until Day 180 visit of all 1600 participants who received first dose and 1577 participants who received second dose.

Demographic characteristics were generally similar among participants across the three groups. Overall, among the participants who received COVISHIELD™, 87.3% were aged 18 to 59 years and 12.7% were 60 years of age or older.

Overall, the incidence of solicited reactions (injection site reactions: pain, tenderness, redness, warmth, itch, swelling and induration; and systemic reactions: fever, chills, fatigue, malaise, headache, arthralgia and myalgia), unsolicited adverse events and serious adverse events (SAEs) was comparable in the study and control groups.

A total of 27 (1.7%) participants reported 27 SAEs, 21 (1.8%) in COVISHIELD™ group, (1.3%) in placebo group and 2 (2·0%) in COVID-19 Vaccine AstraZeneca group. **None of these SAEs were assessed as related to study vaccine. There were no thromboembolic-associated or autoimmune-related SAEs** reported in the study**.**

Table 2 – Adverse drug reactions from COVISHIELD™ study in India

MedDRA SOC	Frequency	Adverse reactions
Gastrointestinal disorders	Common	Nausea
	Uncommon	Diarrhoea
General disorders and administration site conditions	Very common	Injection site pain
	Common	Pyrexia, malaise, fatigue, pain, chills, injection site erythema, injection site swelling, injection site induration, asthenia, injection site pruritus
Musculoskeletal and connective tissue disorders	Common	Myalgia, arthralgia
	Uncommon	Pain in extremity, back pain, neck pain
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, somnolence
Skin and subcutaneous tissue disorders	Uncommon	Urticaria

Summary of post-authorisation data in India

The following adverse reactions were not observed during clinical trials and have been spontaneously reported during post-authorisation use of COVISHIELD™ in India.

Immune system disorders: Anaphylactic reaction (frequency: very rare), Hypersensitivity reactions (frequency: very rare)

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 1/79,830,000. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia (see section 4.4).

Blood and lymphatic system disorders: Thrombocytopenia (frequency: very rare).

Immune thrombocytopenia (frequency: very rare).

Nervous system disorders: Paraesthesia and hypoaesthesia (frequency: very rare).

Facial paralysis (frequency: very rare), Guillain-Barré syndrome (frequency: very rare/ unknown)

Ear and labyrinth disorders: Tinnitus (frequency: very rare).

Skin and subcutaneous tissue disorders: Angioedema (frequency: very rare), cutaneous vasculitis (frequency: very rare).

4.9 Overdose

Experience of overdose is limited.

There is no specific treatment for an overdose with ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant). In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

COVISHIELD™ 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.

Efficacy and immunogenicity data from the Overseas studies:

Clinical efficacy

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

COVID-19 Vaccine AstraZeneca [ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)] has been evaluated based on pooled data from four on-going randomised, blinded, controlled studies: 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 history of anaphylaxis or angioedema; 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). 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 primary analysis for efficacy, participants ≥18 years of age received two doses of COVID-19 Vaccine AstraZeneca (N=8,597) or control (meningococcal vaccine or saline) (N=8,581). Participants randomised to COVID-19 Vaccine AstraZeneca 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 primary analysis, among the participants who received COVID-19 Vaccine AstraZeneca, 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 3056 (35.5%) participants had at least one pre-existing comorbidity (defined as a BMI ≥ 30 kg/m2, 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 143 days and 83 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 332 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. COVID-19 Vaccine AstraZeneca significantly decreased the incidence of COVID-19 compared to control (see Table 2a).

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

Population	COVID-19 Vaccine AstraZeneca		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)	8597	84 (0.98)	8581	248 (2.89)	66.73 (57.41, 74.01)
Licensing regimen					
SDSD	7201	74 (1.03)	7179	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 AstraZeneca 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 AstraZeneca 18/9,335 vs control 63/9,312]).

Exploratory analyses showed that increased vaccine efficacy was observed with increasing dose interval, see Table 2b.

Table 2b - COVID-19 Vaccine AstraZeneca efficacy by dosing interval in COV001, COV002, COV003 and COV005[a]

Dosing interval	COVID-19 Vaccine AstraZeneca		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 (33.0, 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.
[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 AstraZeneca reduced COVID-19 hospitalisation (WHO severity grading ≥4).

In participants who had received two doses of COVID-19 Vaccine AstraZeneca (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).

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 AstraZeneca (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 AstraZeneca (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 AstraZeneca (N=945) compared to 13 for control (N=896), with 0 vs 2 cases in the COVID-19 Vaccine AstraZeneca and control groups, respectively, leading to hospitalisation (WHO severity grading ≥4).

Analysis of efficacy data from D8110C00001

COVID-19 Vaccine AstraZeneca 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 AstraZeneca (N=17,662) or placebo (N=8,550). Participants randomised to COVID-19 Vaccine AstraZeneca 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 AstraZeneca and the placebo groups. Of the participants who received COVID-19 Vaccine AstraZeneca, 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 AstraZeneca 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 AstraZeneca significantly decreased the incidence of COVID-19 compared to placebo (see Table 3).

Table 3 – COVID-19 Vaccine AstraZeneca efficacy against COVID-19[a]

	COVID-19 Vaccine AstraZeneca		Placebo		
	N	Number of COVID-19 cases[b], n (%)	N	Number of COVID-19 cases[b], n (%)	Vaccine efficacy % (95% CI)
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	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	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 AstraZeneca (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 AstraZeneca participants was notably shorter (11 vs 16 days).

Efficacy in subgroups

Participants with one or more comorbidities who received the COVID-19 Vaccine AstraZeneca ≥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 AstraZeneca (≥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].

Updated efficacy analyses

In the 6-month follow-up analysis, updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, with a median follow-up time post second dose of 78 days in participants who received COVID-19 Vaccine AstraZeneca and 71 days in participants who received placebo. Overall vaccine efficacy against

symptomatic COVID-19 illness was 66.98% (95% CI: 58.87, 73.50) with 141 (0.80%) cases of COVID-19 reported in participants who had received two doses of COVID-19 Vaccine AstraZeneca (N=17,617) and 184 (2.16%) cases reported in participants who had received placebo (N=8,528). In participants ≥65 years old there were 6 (0.16%) cases reported in the COVID-19 Vaccine AstraZeneca group (N=3,696) compared with 19 (1.05%) cases in the placebo group (N=1,816), corresponding to a vaccine efficacy of 86.35% (95% CI: 65.79, 94.55).

In individuals with or without prior evidence of SARS-CoV-2 infection, vaccine efficacy against symptomatic COVID-19 illness was 66.96% (95% CI: 58.94, 73.41) with 144 (0.78%) versus 189 (2.11%) cases of COVID-19 in the COVID-19 Vaccine AstraZeneca (N=18,450) and placebo (N=8,960) groups, respectively.

Against severe or critical symptomatic COVID-19 illness, vaccine efficacy was 95.69% (95% CI: 66.33, 99.45) with 1 (0.01%) case reported in the COVID-19 Vaccine AstraZeneca group (N=17,617) and 10 (0.12%) cases reported in the placebo group (N=8,528). There were 2 (0.01%) versus 15 (0.18%) cases of COVID-19-related emergency department visits in the COVID-19 Vaccine AstraZeneca (N=17,617) and placebo (N=8,528) groups, respectively, corresponding to a vaccine efficacy of 94.17% (95% CI: 74.49, 98.67).

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 (1.67%) SARS-CoV-2 infections in the COVID-19 Vaccine AstraZeneca group (N=17,617) and 323 (3.79%) infections in the placebo group (N=8,528), corresponding to a vaccine efficacy of 61.01% (95% CI: 54.35; 66.70).

Immunogenicity

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

Following vaccination with COVID-19 Vaccine AstraZeneca, 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 4).

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 4 – SARS CoV-2 S-binding antibody response to COVID-19 Vaccine AstraZeneca[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=1538) 57.1 (53.8, 60.6)	(N=1466) 8358.0 (7879.2, 8866.0)	(N=1511) 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=18759.6 [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 (Table 3). The majority of participants ≥65 years old had a dose interval of <6 weeks, which may have contributed to the numerically 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-ɣ enzyme-linked immunospot (ELISpot) assay are induced after a first dose of COVID-19 Vaccine AstraZeneca. 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 AstraZeneca with cells expressing IFN-γ, IL-2, and/or TNFα which are generally similar between

age categories.

Study D7220C00001, immunogenicity of a booster dose following primary vaccination with COVID-19 Vaccine AstraZeneca *or an mRNA COVID-19 vaccine*

D7220C00001 is a phase II/III partially double-blind, active-controlled study in which 367 participants ≥18 years old previously vaccinated with COVID-19 Vaccine AstraZeneca and 322 participants ≥18 years old previously vaccinated with an mRNA vaccine received a single booster dose of COVID-19 Vaccine AstraZeneca at least 90 days after receiving the second dose of their primary vaccination course. Immunogenicity was assessed in 342 participants previously vaccinated with COVID-19 Vaccine AstraZeneca and 294 participants previously vaccinated with an mRNA vaccine, all of whom were seronegative at baseline. Participants previously vaccinated with COVID-19 Vaccine AstraZeneca were older than participants previously vaccinated with an mRNA vaccine with 45.9% and 26.9% being ≥65 years of age in the two groups, respectively. Approximately 47% of the participants had at least one pre-existing comorbidity (defined as BMI ≥30 kg/m2, significant cardiovascular disease, chronic lung disease, or diabetes).

The effectiveness of COVID-19 Vaccine AstraZeneca administered as a single booster dose in participants previously vaccinated with COVID-19 Vaccine AstraZeneca was demonstrated by evaluating non-inferiority of the immune response of neutralising 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 neutralising antibody titres 28 days after the booster dose to titres 28 days after the primary vaccination course (see Table 5).

Table 5: Neutralising antibody titres against the ancestral strain following booster dosing with COVID-19 Vaccine AstraZeneca in participants previously vaccinated with COVID-19 Vaccine AstraZeneca

	28 days after primary vaccination course with COVID-19 Vaccine AstraZeneca[a]	**28 days after booster dose**	**GMT ratio[b]**	**Met non-inferiority objective (Y/N)**
n	508	327	327/508	
GMT [c]	242.80	248.89	1.03	Y[d]
(95% CI)	(224.82, 262.23)	(229.53, 269.89)	(0.92, 1.15)	

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

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

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

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

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

COVID-19 Vaccine AstraZeneca was also shown to be effective in eliciting antibody responses in

participants who had previously received primary vaccination with an mRNA vaccine. In these participants, a single booster dose of COVID-19 Vaccine AstraZeneca resulted in increased humoral responses, with geometric mean fold rise (GMFR) of 3.77 (95% CI: 3.26, 4.37) in neutralising antibody titres against the ancestral strain from pre-booster to 28 days after the booster dose.

Booster dosing with COVID-19 Vaccine AstraZeneca increased humoral responses also in participants with serological evidence of prior SARS-CoV-2 infection at baseline, and against all analysed variants, i.e. Alpha, Beta, Gamma, Delta and Omicron.

COV001 Immunogenicity of a booster dose (third dose) following primary vaccination with COVID-19 Vaccine AstraZeneca

COV001 included 90 participants aged 18-55 years who received a booster dose with COVID-19 Vaccine AstraZeneca. 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).

RHH-001 immunogenicity of a booster dose (third dose) following primary vaccination with an inactivated whole-virion COVID-19 vaccine

The externally sponsored RHH-001 was a phase IV single-blind, randomised study, in which antibodies were assessed in 296 Brazilian participants >18 years old who received a booster dose of COVID-19 Vaccine AstraZeneca 5-7 months after receiving the second dose of an inactivated whole-virion COVID-19 vaccine.

At 28 days after receipt of a booster dose of COVID-19 Vaccine AstraZeneca there was a substantial increase from baseline in spike IgG antibody titres (Day 28 GMT 335213 [95% CI: 295598, 380136], baseline GMT 3745 [95% CI: 3252, 4313]). The GMFR from baseline to Day 28 was 90 (95%, CI: 77, 104). Participants who had received a booster dose of COVID-19 Vaccine AstraZeneca had spike IgG antibody titres at Day 28 that were statistically superior to those induced by a booster dose of the inactivated whole-virion COVID-19 vaccine. Geometric mean ratio (GMR) for COVID-19 Vaccine AstraZeneca booster dose versus the inactivated COVID-19 vaccine booster dose was 7.0 (95% CI 6.1, 8.1, p<0,0001). Booster dosing with COVID-19 Vaccine AstraZeneca also increased neutralisation antibody titres against the Delta and Omicron variants.

Immunogenicity data from the Indian study:

GMTs of IgG antibodies against spike (S) protein were comparable between the groups at baseline – Day 1. GMTs increased significantly after each dose of vaccine in both the groups

and were comparable. There was > 98% seroconversion in both the groups on Day 57. The immunogenicity data indicates that COVISHIELD™ is comparable in terms of anti-S IgG antibody titers and seroconversion rates to COVID-19 Vaccine AstraZeneca (see Tables 6 and 7).

Table 6 Summary of Anti-S IgG antibodies

Timepoint	Statistic	COVISHIELD™ (N=297) n (%)	COVID-19 Vaccine AstraZeneca (N=98)
Baseline	N	297	98
	GMT	95.4	79.4
	95% CI	(78.1, 116.6)	(58.2, 108.4)
28 days after Dose 1	N	295	98
	GMT	10131.1	6660.8
	95% CI	(8473.2, 12007.9)	(4836.3, 9173.7)
28 days after Dose 2	n	293	95
	GMT	30245.6	28558.3
	95% CI	(26794.0, 34141.8)	(23479.3, 34735.8)
180 days after Dose 1	n	258	88
	GMT	10134.2	15539.2
	95% CI	(8497.4, 12086.4)	(10317.1, 23404.4)

Table 7 Summary of Proportion of Participants with Seroconversion for Anti-S IgG Antibodies

Timepoint	Statistic	COVISHIELD™ (N=297)	COVID-19 Vaccine AstraZeneca (N=98)
28 days after Dose 1	N Evaluated	295	98
	Seroconversion, n (%)	285 (96.6)	90 (91.8)
	95% CI	(93.9, 98.4)	(84.5, 96.4)
28 days after Dose 2	N Evaluated	293	95
	Seroconversion, n (%)	287 (98.0)	94 (98.9)
	95% CI	(95.6, 99.2)	(94.3, 100.0)
180 days after Dose 1	N Evaluated	258	88
	Seroconversion, n (%)	243 (94.2)	85 (96.6)

Timepoint	Statistic	COVISHIELD™ (N=297)	COVID-19 Vaccine AstraZeneca (N=98)
	95% CI	(90.6, 96.7)	(90.4, 99.3)

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 AstraZeneca 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 AstraZeneca related inflammation.

Mutagenicity and carcinogenicity

ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) 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 AstraZeneca to the gonads (testes, ovaries) following IM injection.

In a reproductive and development toxicity study, COVID-19 Vaccine AstraZeneca 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.

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

The expiry date of vaccine is indicated on the label and packaging.

Once opened, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2ºC and +25ºC. All opened multidose vials of **COVISHIELD™** should be discarded at the end of immunization session or within six hours whichever comes first.

6.4 Special precautions for storage

Store in a refrigerator (+2ºC to +8ºC). Do not freeze. Keep vials in outer carton to protect from light. Discard if vaccine has been frozen.

Opened multidose vial (After first use)

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

6.5 Nature and contents of container

COVISHIELD™ is supplied as ready to use liquid in rubber-stoppered multidose vial and single dose vial in below listed presentations

1 dose – 0.5 mL per vial
2 dose – 1.0 mL per vial
5 dose – 2.5 mL per vial
10 dose – 5.0 mL per vial
20 dose – 10 mL per vial

6.6 Instructions for use, handling and disposal

Administration

COVISHIELD™ is a colourless to slightly brown, clear to slightly opaque solution. 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.

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. 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. Aseptic technique should be used for withdrawing the dose for administration.

After first opening, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2ºC and +25ºC. Discard any unused vaccine.

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

Disposal

COVISHIELD™ 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 (e.g. Hydrogen peroxide-based disinfectants).

7 MARKETING AUTHORIZATION

Serum Institute of India Pvt. Ltd.
S. No. 105-110, Manjari, Budruk, Pune, Maharashtra 412307

Marketed by:

SERUM INSTITUTE LIFE SCIENCES PVT. LTD.
401, Sarosh Bhavan, 16-B/1, Dr. Ambedkar Road, Pune - 411 001, INDIA

8 MARKETING AUTHORISATION NUMBER (S)

MF/BIO/21/000019; Dated 27 January 2022

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of First Authorization: 27 January 2022

Trademark under registration