For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

SII

SARS-CoV-2 rS Protein (COVID-19) recombinant spike protein Nanoparticle Vaccine

COVOVAX™

1 NAME OF THE MEDICINAL PRODUCT
Trade/Brand Name: COVOVAX™
SARS-CoV-2 rS Protein (COVID-19) recombinant spike protein Nanoparticle Vaccine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One dose (0.5 ml) contains 5 micrograms of SARS-CoV-2 spike protein* and is adjuvanted with 50 micrograms of Matrix-M1.
Adjuvant Matrix-M1 containing per 0.5 ml dose: Fraction-A (42.5 micrograms) and Fraction-C (7.5 micrograms) of *Quillaja saponaria* Molina extract.
* SARS-CoV-2 recombinant spike protein is produced by recombinant DNA technology using a baculovirus expression system in an insect cell line that is derived from Sf9 cells of the *Spodoptera frugiperda* species.
For the full list of excipients, see section 6.1.
Both **COVOVAX™** (manufactured by Serum Institute of India Pvt Ltd) and Novavax COVID-19 vaccine (manufactured by Novavax) are SARS-CoV-2 rS Protein (COVID-19) Nanoparticle Vaccines.

3 PHARMACEUTICAL FORM
Dispersion for injection (injection).
COVOVAX™ is colourless to slightly yellow, clear to mildly opalescent, free to practically free from visible particles.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
COVOVAX™ is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 7 years of age and older.
The vaccine is approved for restricted use in emergency situation that may prevent COVID-19 disease.

4.2 Posology and method of administration
Posology
Primary Series
Individuals 7 years of age and older
COVOVAX™ is administered intramuscularly as a course of 2 doses of 0.5 ml each. It is recommended to administer the second dose 3 weeks after the first dose, see section 5.1.
It is recommended that individuals who receive a first dose of **COVOVAX™**, complete the vaccination course with **COVOVAX™**.
Booster dose
Individuals 18 years of age and older
A booster dose of COVOVAX™ may be administered intramuscularly approximately 6 months after completion of the second dose in the primary series [ChAdOx1 nCov-19 Corona Virus Vaccine (Recombinant) / Whole Virion, Inactivated Coronavirus (SARS-CoV-2) Antigen] in individuals 18 years of age and older.
Paediatric population
The safety and immunogenicity of SARS-CoV-2 rS Protein (COVID-19) Nanoparticle Vaccine in children aged 2 to 6 years has been established and is under evaluation.
Elderly population
No dose adjustment is required in elderly individuals ≥ 65 years of age.
Method of administration
COVOVAX™ is intended for Intramuscular (IM) injection only, preferably in the deltoid muscle. If deltoid muscle mass is small, injection can be given in the anterolateral thigh 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.

4.4 Special warnings and precautions for use
Hypersensitivity and anaphylaxis
Events of anaphylaxis have been reported with COVID-19 vaccines. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.
Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of **COVOVAX.™**
Myocarditis and Pericarditis
Myocarditis and pericarditis have been reported in male and female adults within 14 days of administering Novavax COVID-19 Vaccine (recombinant, adjuvanted). (see section 4.8).
Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.
Available data cannot determine a causal association with Novavax COVID-19 Vaccine (recombinant, adjuvanted). Vaccinated individuals (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.
The risk of myocarditis and pericarditis after a third dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) has not yet been characterized.
Anxiety-related reactions
Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation, or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.
Concurrent illness
Vaccination should be postponed in individuals suffering from an acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.
Thrombocytopenia and coagulation disorders
As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur at the injection site following an intramuscular administration in these individuals.
Immunocompromised individuals
There is no data on efficacy, safety, and immunogenicity of COVOVAX™ in immunocompromised individuals.
Duration of protection
The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.
Limitations of vaccine effectiveness
Individuals may not be fully protected until 7 days after their second dose. As with all vaccines, vaccination with **COVOVAX™** may not protect all vaccine recipients.
Excipients
Sodium
This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
Potassium
This vaccine contains potassium, less than 1 mmol (39 mg) per 0.5 ml, that is to say, essentially 'potassium-free'.

4.5 Interaction with other medicinal products and other forms of interaction
Co-administration of SARS-CoV-2 rS Protein (COVID-19) Nanoparticle Vaccine with inactivated influenza vaccines has been evaluated in a limited number of participants in an exploratory Novavax clinical trial sub-study 2019nCoV-302, see section 4.8 and section 5.1.
The binding antibody response to SARS-CoV-2 was lower when Novavax COVID-19 vaccine was given concomitantly with inactivated influenza vaccine. The clinical significance of this is unknown.
Concomitant administration of SARS-CoV-2 rS Protein (COVID-19) Nanoparticle Vaccine with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation
Pregnancy
There is limited experience with use of Novavax COVID-19 Vaccine (recombinant, adjuvanted) in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or post-natal development, see section 5.3.
Administration of **COVOVAX™** in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.
Breast-feeding
Data is not available to assess the effects of SARS-CoV-2 rS Protein (COVID-19) Nanoparticle Vaccine on the breastfed infant or on milk production/excretion.
Fertility
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, see section 5.3.

4.7 Effects on ability to drive and use machines
COVOVAX™ has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
Overall summary of the safety profile from the Overseas studies:
Clinical trial data for the age group ≥ 18 Years after two-dose primary series:
The safety of Novavax COVID-19 vaccine [Novavax SARS-CoV-2 rS Protein (COVID-19) Nanoparticle Vaccine] was evaluated from an interim analysis of pooled data from 5 ongoing clinical trials conducted in Australia, South Africa, the United Kingdom, the United States and Mexico. At the time of the analysis, a total of 49,950 participants age 18 years and older received at least one dose of Novavax COVID-19 vaccine (n=30,058) or placebo (n=19,892). At the time of vaccination, the median age was 48 years (range 18 to 95 years).
The median duration of follow-up was 70 days post-Dose 2, with 32,993 (66%) participants completing more than 2 months follow-up post-Dose 2.
Of the pooled reactogenicity data, which includes participants age 18 years and older enrolled in the two phase 3 studies who received at least one dose of Novavax COVID-19 vaccine (n = 20,055) or placebo (n = 10,561), the most frequent adverse reactions were injection site tenderness (75%), injection site pain (62%), fatigue (53%), myalgia (51%), headache (50%), malaise (41%), arthralgia (24%), and nausea or vomiting (15%). Adverse reactions were usually mild to moderate in severity with a median duration of less than or equal to 2 days for local events and less than or equal to 1 day for systemic events following vaccination.
Adolescents 12 through 17 years of age - after two-dose primary series
The safety of Novavax COVID-19 Vaccine (recombinant, adjuvanted) in adolescents was evaluated in an interim analysis of the pediatric expansion portion of an ongoing Phase 3 multicenter, randomized, observer-blinded, placebo-controlled study (Study 2019nCoV-301).
Safety data was collected in 2,232 participants 12 through 17 years of age, with and without evidence of prior SARS CoV-2 infection, in United States who received at least one dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) (n=1,487) and placebo (n=745).
Demographic characteristics were similar among participants who received Novavax COVID-19 Vaccine (recombinant, adjuvanted) and those who received placebo.
The most frequent adverse reactions were injection site tenderness (71%), injection site pain (67%), headache (63%), myalgia (57%), fatigue (54%), malaise (43%), nausea or vomiting (23%), arthralgia (19%) and pyrexia (17%). Adverse reactions were usually mild to moderate in severity with a median duration of less than or equal to 2 days for local events and less than or equal to 1 day for systemic events following vaccination.
Participants 18 years of age and older - after booster dose
The safety and immunogenicity of a booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) was evaluated in an ongoing Phase 2 randomized, placebo-controlled, observer-blinded clinical study (Study 2019nCoV-101, Part 2) conducted in participants aged 18 to 84 years of age. A total of 254 participants received two doses of Novavax COVID-19 Vaccine (recombinant, adjuvanted) (0.5 mL 3 weeks apart) as the primary vaccination series. A subset of 104 participants (Full Analysis Set) received a booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) approximately 6 months after receiving Dose 2 of the primary series.
The most frequent solicited adverse reactions were injection site tenderness (81%), fatigue (63%), injection site pain (55%), muscle pain (51%), malaise (47%) and headache (46%), joint pain (29%), and fever (17%) with a median duration of 1 to 3 days following vaccination.
Tabulated list of adverse reactions
Very common (≥ 1/10),
Common (≥ 1/100 to < 1/10),
Uncommon (≥ 1/1,000 to < 1/100),
Rare (≥ 1/10,000 to < 1/1,000),
Very rare (< 1/10,000),
Not known (cannot be estimated from the available data).

Table 1: Adverse reactions from Novavax COVID-19 vaccine Clinical Trials in individuals 12 years of age and older

MedDRA SOC	Frequency	Adverse reactions
General disorders and administration site conditions	Very common	Injection site pain[a], injection site tenderness[a], fatigue[a], malaise[a,b]
	Common	Injection site redness[c], injection site swelling, pyrexia, chills, pain in extremity
	Uncommon	Injection site pruritis
Nervous system disorders	Very common	Headache
Musculoskeletal and connective tissue disorders	Very common	Myalgia[a], arthralgia[a]
Gastrointestinal system disorders	Very common	Nausea or vomiting[a]
Skin and subcutaneous tissue disorders	Uncommon	Rash, erythema, pruritus, urticaria
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy

[a] Higher frequencies of these events were observed after the second dose.
[b] This term also included events reported as influenza-like illness.
[c] This term includes both injection site redness and injection site erythema (common).

Overall summary of the safety profile from the Indian studies
ICMR/SII-COVOVAX Study:
Adult cohort (≥18 years of age):
COVOVAX™ was safe and well tolerated in the phase 2/3 clinical trial in India. In the Phase 2 part (n=200), 200 adults received **COVOVAX™** or Placebo in 3:1 ratio. In the Phase 3 part (n=1396), participants received **COVOVAX™** or Novavax SARS-CoV-2 rS Protein Nanoparticle Vaccine (Novavax vaccine) in 3:1 ratio [1046 in **COVOVAX™** group and 350 in Novavax SARS-CoV-2 rS Protein Nanoparticle Vaccine (Novavax vaccine) group]. All 1396 participants received the first dose while 1375 participants received the second dose. The final analysis included data collected throughout entire study (179 days after the first dose).
Demographic characteristics were generally similar among participants across both the groups.
Overall, the incidence of solicited reactions (injection site reactions: pain, tenderness, erythema, swelling and induration; and systemic reactions: fever, headache, fatigue, malaise, arthralgia, myalgia, nausea and vomiting), unsolicited adverse events and serious adverse events (SAEs) was comparable in the study and control groups.
There were no causally related serious adverse events (SAEs) reported throughout the entire study.

Table 2: Adverse drug reactions from COVOVAX™ study in adults in India

MedDRA SOC	Frequency	Adverse reactions
Gastrointestinal disorders	Common	Nausea
	Uncommon	Vomiting
General disorders and administration site conditions	Very common	Injection site pain, pyrexia
	Common	Injection site tenderness, injection site erythema, injection site swelling, injection site induration, fatigue, pain, malaise
	Uncommon	Asthenia, injection site pruritus
	Rare	Chills, injection site rash
Musculoskeletal and connective tissue disorders	Common	Myalgia, arthralgia
	Uncommon	Pain in extremity, back pain
Nervous system disorders	Very common	Headache
	Rare	Dizziness, somnolence
Skin and subcutaneous tissue disorders	Rare	Pruritus

Pediatric cohort (≥ 2 to < 18 years of age):
This is a Phase 2/3, observer-blind, randomized, controlled study in 920 Indian children 2 to 17 years of age, to evaluate the safety and immunogenicity of **COVOVAX™**.

Pediatric cohort (≥12 to <18 years of age):
A total of 460 children of ≥ 12 to < 18 years of age received the first dose of study vaccine (346 **COVOVAX™** and 114 Placebo) and 445 received the second dose of study vaccine (335 **COVOVAX™** and 110 Placebo). Demographic characteristics were generally similar among participants across both the groups.
COVOVAX™ was well tolerated with an acceptable safety profile. Pain (36.4%) and tenderness (11.3%) were the most frequent solicited local adverse events. Fever (22.5%), headache (18.8%), fatigue (14.2%), and malaise (9.2%) and were the most frequent solicited systemic adverse events. The local and systemic solicited events were mostly of mild severity with median duration of 1 to 2 days.

Table 3: Adverse drug reactions in pediatric cohort (≥ 12 to < 18 years of age) from COVOVAX™ study in India

MedDRA SOC	Frequency	Adverse reactions
General disorders and administration site conditions	Very common	Injection site pain, injection site tenderness, fatigue, pyrexia
	Common	Injection site erythema, injection site swelling, injection site induration, malaise
Nervous system disorders	Very common	Headache
Musculoskeletal and connective tissue disorders	Common	Myalgia, Arthralgia
Gastrointestinal system disorders	Common	Nausea, vomiting

Pediatric cohort (≥ 2 to < 12 years of age):
A total of 460 children of ≥2 to <12 years of age received the first dose of study vaccine (345 **COVOVAX™** and 115 Placebo) and 445 received the second dose of study vaccine (333 **COVOVAX™** and 112 Placebo). Demographic characteristics were generally similar among participants across both the groups.
COVOVAX™ was well tolerated with an acceptable safety profile. Pain (34.8%) and tenderness (11.9%) were the most frequent solicited local adverse events. Fever (37.4%), and headache (14.5%) were the most frequent solicited systemic adverse events. The local and systemic solicited events were mostly of mild severity with median duration of 1 to 2 days.

Table 4: Adverse drug reactions in pediatric cohort (≥ 2 to < 12 years of age) from COVOVAX™ study in India.

MedDRA SOC	Frequency	Adverse reactions
General disorders and administration site conditions	Very common	Injection site pain, injection site tenderness, pyrexia
	Common	Injection site swelling, injection site erythema, injection site induration, malaise, fatigue
Nervous system disorders	Very common	Headache
Musculoskeletal and connective tissue disorders	Common	Myalgia, Arthralgia
Gastrointestinal system disorders	Common	Nausea, vomiting

COVOVAX-Booster study in adults:
This is an ongoing Phase 3, observer-blinded, randomised, active controlled study in adults ≥ 18 years of age in India who had already received primary vaccination against COVID-19 at least 6 months ago (6 months / 180 days from the second dose). A total of 186 participants each in the Covishield Prime cohort and the Covaxin Prime cohort received study vaccines i.e. either COVOVAX or Covishield [ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant), a replication deficient, chimpanzee adenovirus vectored vaccine] in the Covishield prime cohort and COVOVAX or Covaxin [Whole Virion Inactivated Coronavirus (SARS-CoV-2) Vaccine] in the Covaxin prime cohort, respectively.
COVOVAX was well tolerated with an acceptable safety profile as a heterologous booster. Pain (18.5% and 21.7% in the Covishield and the Covaxin Prime cohorts, respectively) and tenderness (5.4% and 4.3% in the Covishield and the Covaxin Prime cohorts, respectively) were the most frequent solicited local adverse events. Headache (13%), arthralgia (7.6%) and fatigue (7.6%) were the most frequent solicited systemic adverse events in the Covishield Prime cohort. Fatigue (12%), headache (14.1%) and malaise (13%) were the most frequent solicited systemic adverse events in the Covaxin Prime cohort. The local and systemic solicited events were mostly of mild severity with median duration of 1 to 2 days.

Table 5: Adverse drug reactions from COVOVAX booster study in adults in India

MedDRA SOC	Frequency	Adverse reactions	
		Covishield Prime cohort	Covaxin Prime cohort
General disorders and administration site conditions	Very common	Injection site pain	Injection site pain, fatigue, malaise
	Common	Injection site tenderness, injection site erythema, injection site swelling, injection site induration, malaise, fatigue, pyrexia	Injection site tenderness, injection site erythema, injection site swelling, injection site induration, pyrexia
Nervous system disorders	Very common	Headache	Headache
Musculoskeletal and connective tissue disorders	Common	Myalgia, Arthralgia	Myalgia, Arthralgia
Gastrointestinal system disorders	Common	Nausea, vomiting	Nausea, vomiting

Post-marketing experience
The following adverse reactions have been reported during post-authorization use of Novavax COVID-19 Vaccine (recombinant, adjuvanted). The frequencies could not be determined and are thus considered as not known.

Table 6 lists the post-marketing experience adverse reactions from Novavax COVID-19 Vaccine (recombinant, adjuvanted).

MedDRA SOC	Frequency	Adverse reactions
Nervous system disorders	Not known	Paraesthesia and hypoaesthesia
Immune system disorder	Not known	Anaphylaxis
Cardiac disorders	Not known	Myocarditis and pericarditis

4.9 Overdose
No case of overdose has been reported. In the event of an overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other viral vaccines, ATC code: J07BX03
Mechanism of action
COVOVAX™ is composed of purified full-length SARS-CoV-2 recombinant spike (S) protein that is stabilised in its prefusion conformation. The addition of the saponin-based Matrix-M1 adjuvant facilitates activation of the cells of the innate immune system, which enhances the magnitude of the S protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the S protein, including neutralising antibodies, which protect against COVID-19.
Efficacy data from the Overseas studies:
The clinical efficacy, safety, and immunogenicity of Novavax COVID-19 Vaccine is being evaluated in two pivotal, placebo-controlled, Phase 3 studies, Study 1 (2019nCoV-301) conducted in North America and Study 2 (2019nCoV-302) conducted in the United Kingdom.
Study 1 (2019nCoV-301) - Two-Dose Primary Series
Study 1 is an ongoing Phase 3, multicentre, randomised, observer-blinded, placebo-controlled study with an adult main study conducted in participants 18 years of age and older in United States and Mexico, and a pediatric expansion occurring in participants 12 through 17 years of age in the United States.
Participants 18 years of age and older
Upon enrolment in the adult main study, participants were stratified by age (18 to 64 years and ≥ 65 years) and assigned in a 2:1 ratio to receive Novavax COVID-19 Vaccine or placebo.
The primary efficacy analysis population (referred to as the Per-Protocol Efficacy [PP-EFF] analysis set) included 25,452 participants who received either Novavax COVID-19 Vaccine (n=17,312) or placebo (n=8,140), received two doses (Dose 1 on day 0; Dose 2 at days 21, did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through 7 days after the second dose.
Demographic and baseline characteristics were balanced amongst participants who received Novavax COVID-19 Vaccine and those who received placebo.
The vaccine efficacy is presented in Table 7.

Table 7: Vaccine efficacy against PCR-confirmed COVID-19 with onset from 7 days after second vaccination[1] - PP-EFF analysis set; Study 2019nCoV-301

Subgroup	Novavax COVID-19 Vaccine			Placebo			% Vaccine Efficacy (95% CI)
	Participants N	COVID-19 cases n (%)[2]	Incidence Rate Per Year Per 1,000 People[2]	Participants N	COVID-19 cases n (%)[3]	Incidence Rate Per Year Per 1,000 People[2]	
Primary efficacy endpoint							
All participants	17,312	14 (0.1)	3.26	8,140	63 (0.8)	34.01	90.4% (82.9, 94.6)[3,4]
Mild	-	14 (0.1)	-	-	49 (0.6)	-	-
Moderate	-	0	-	-	10 (0.1)	-	-
Mild	-	0	-	-	4 (< 0.1)	-	-

1 VE evaluated in participants without major protocol deviation who are seronegative (for SARS-CoV-2) at baseline and do not have a laboratory confirmed current SARS-CoV-2 infection with symptom onset up to 6 days after the second dose, and who have received the full prescribed regimen of trial vaccine.
2 Mean disease incidence rate per year in 1,000 people.
3 Based on log-linear model of PCR-confirmed COVID-19 infection incidence rate using Poisson regression with treatment group and age strata as fixed effects and robust error variance, where VE = 100 × (1 - relative risk) (Zou 2004).
4 Met primary efficacy endpoint criterion for success with a lower bound confidence interval (LBCI) > 30% at the planned primary confirmatory analysis

Efficacy in Adolescents 12 through 17 years of age
The assessment of efficacy and immunogenicity of Novavax COVID-19 Vaccine (recombinant, adjuvanted) in adolescent participants 12 through 17 years of age occurred in the United States in the ongoing pediatric expansion portion of the Phase 3 multicenter, randomized, observer-blinded, placebo-controlled 2019nCoV-301 study.
A total of 1,799 participants assigned in a 2:1 ratio to receive two doses of Novavax COVID-19 Vaccine (recombinant, adjuvanted) (n=1,205) or placebo (n=594) by intramuscular injection 21 days apart represented the primary efficacy population.
COVID-19 was defined as first episode of PCR-confirmed mild, moderate, or severe COVID-19 with at least one or more of the predefined symptoms within each severity category. There were 20 cases of PCR-confirmed symptomatic mild COVID-19 (Novavax COVID-19 Vaccine (recombinant, adjuvanted), n=6; placebo, n=14) resulting in a point estimate of efficacy of 79.5% (95% CI: 46.8%, 92.1%).
At the time of this analysis, the Delta (B.1.617.2 and AY lineages) variant of concern (VOC) was the predominant variant circulating in the US and accounted for all cases where sequence data are available (11/20, 55%).
Immunogenicity in Adolescents 12 through 17 years of age
An analysis of the SARS-CoV-2 neutralizing antibody response 35 days after Dose 2 was conducted in adolescent participants seronegative to anti-SARS-CoV-2 nucleoprotein (NP)/PCR-negative at baseline compared with that observed in seronegative/PCR-negative adult participants aged 18 to less than 26 years from the adult main study (Per Protocol Immunogenicity (PPIMM) Population, before crossover). Noninferiority (lower bound 95% CI for the geometric mean ratio [GMR] >0.67 [1.25]) was met as presented in Table 7.

Table 8: Adjusted Ratio of Geometric Mean of Microneutralization Assay Neutralizing Antibody Titers for SARS-CoV-2 S Wild-Type Virus at Day 35 Overall and Presented by Age Group (PPIMM Analysis Set)[1]

Assay	Timepoint	Pediatric Expansion (12 to 17 years) N=390	Adult Main Study (18 to < 26 years) N=416	12 to 17 years Vs. 18 to < 26 years
		GMT 95% CI[2]	GMT 95% CI[2]	GMT 95% CI[2]
Microneutralization assay (1/dilution)	35 days after dose 2	3859.6 (3422.8, 4352.1)	2633.6 (2388.6, 2903.6)	1.46 (1.25, 1.71)[3]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMR = ratio of GMT, which is defined as the ratio of 2 GMTs for comparison of 2 age cohorts; GMT = geometric mean titer; LLOQ = lower limit of quantitation; MN = microneutralization; N = number of participants in assay-specific PP-IMM Analysis Set in each part of study with non-missing response at each visit; PP-IMM = Per-Protocol Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus2.
1 Table includes participants in the active vaccine group only.
2 An ANCOVA with age cohort as main effect and baseline MN Assay neutralizing antibodies as covariate was performed to estimate the GMR. Individual response values recorded as below the LLOQ were set to half LLOQ.
3 Represents (n1, n2) populations defined as:
n1 = number of participants in adult main study (18 to < 26 years) with non-missing neutralizing antibodies result
n2 = number of participants in pediatric expansion (12 to <18 years) with non-missing neutralizing antibodies result

Study 2 (2019nCoV-302) - Two-Dose Primary Series
Study 2 is an ongoing Phase 3, multicentre, randomised, observer-blinded, placebo-controlled study in participants 18 to 84 years of age in the United Kingdom. Upon enrolment, participants were stratified by age (18 to 64 years; 65 to 84 years) to receive Novavax COVID-19 Vaccine or placebo.
The primary efficacy analysis set (PP-EFF) included 14,039 participants who received either Novavax COVID-19 Vaccine (n= 7,020) or placebo (n= 7,019), received two doses (Dose 1 on day 0; Dose 2 at median 21 days) did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through 7 days after the second dose.
Demographic and baseline characteristics were balanced amongst participants who received Novavax COVID-19 Vaccine and participants who received placebo.
Vaccine efficacy is presented in Table 9.

Table 9: Vaccine efficacy analysis of PCR-confirmed COVID-19 with onset at least 7 days after the second vaccination - (PP-EFF population): Study 2 (2019nCoV-302)

Subgroup	Novavax COVID-19 vaccine			Placebo			% Vaccine Efficacy (95% CI)
	Participants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[1]	Participants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[1]	
Primary efficacy endpoint							
All participants	7,020	10 (0.1)	6.53	7,019	96 (1.4)	63.43	89.7% (80.2, 94.6)[2,3]
Mild	–	1 (< 0.1)	–	–	28 (0.4)	–	–
Moderate	–	9 (0.1)	–	–	63 (0.9)	–	–
Severe	–	0	–	–	5 (< 0.1)	–	–
Subgroup analyses of the primary efficacy endpoint							
18 to 64 years of age	5,067	9 (0.2)	12.30	5,062	87 (1.7)	120.22	89.8% (79.7, 94.9)[2]
65 to 84 years of age	1,953	1 (0.10)[2]	----	1,957	9 (0.9)[2]	----	88.9% (20.2, 99.7)[4]

1 Mean disease incidence rate per year in 1000 people.
2 Based on Log-linear model of occurrence using modified Poisson regression with logarithmic link function, treatment group and strata (age-group and pooled region) as fixed effects and robust error variance [Zou 2004].
3 Met primary efficacy endpoint criterion for success with a lower bound confidence interval (LBCI) > 30% efficacy has been confirmed at the interim analysis.
4 Based on the Clopper-Pearson model (due to few events), 95% CIs calculated using the Clopper-Pearson exact binomial method adjusted for the total surveillance time.

Vaccine efficacy of Novavax COVID-19 Vaccine (recombinant, adjuvanted) to prevent the onset of COVID-19 from seven days after Dose 2 was 89.7% (95% CI 80.2 - 94.6). No cases of severe COVID-19 were reported in the 14,039 Novavax COVID-19 Vaccine (recombinant, adjuvanted) participants compared with 5 cases of severe COVID-19 reported in the 7,019 placebo recipients in the PP-EFF analysis set.
These results reflect enrolment that occurred during the time period when the B.1.17 (Alpha) variant was circulating in the UK. Identification of the Alpha variant was based on S gene target failure by PCR.
No cases of severe COVID-19 were reported in the 7,020 Novavax COVID-19 Vaccine participants compared with 4 cases of severe COVID-19 reported in the 7,019 placebo recipients in the PP-EFF analysis set.
Licensed seasonal influenza vaccine co-administration sub-study
Overall, 431 participants were co-vaccinated with inactivated seasonal influenza vaccines; 217 sub-study participants received Novavax COVID-19 Vaccine and 214 received placebo. Demographic and baseline characteristics were balanced amongst participants who received Novavax COVID-19 vaccine and participants who received placebo. Co-administration resulted in no change to influenza vaccine immune responses as measured by hemagglutination inhibition (HAI) assay. A reduction in antibody responses to Novavax COVID-19 Vaccine was noted as assessed by an anti-spike IgG assay with seroconversion rates similar to participants who did not receive concomitant influenza vaccine. (see section 4.5 and section 4.8).
Immunogenicity in participants 18 years of age and older - after booster dose
Study 2019nCoV-101, Part 2 (USA and Australia)
The safety and immunogenicity of a booster dose of Novavax COVID-19 Vaccine was evaluated in an ongoing Phase 2 randomized, observer-blinded, placebo-controlled clinical study administered as a single booster dose (Study 2019nCoV-101, Part 2) in healthy adult participants aged 18 to 84 years of age who were seronegative to SARS-CoV-2 at baseline.
A total of 254 participants (Full Analysis Set) received two doses of Novavax COVID-19 Vaccine (0.5 mL, 3 weeks apart) as the primary vaccination series. A subset of 104 participants received a booster dose of Novavax COVID-19 Vaccine approximately 6 months after receiving Dose 2 of the primary series.
A single booster dose of Novavax COVID-19 Vaccine induced an approximate 31-fold increase in the immune response against the Wuhan (ancestral) strain 28 days after receipt of the dose (Day 217) with serum IgG geometric mean titer (GMT) of 204,367 EU compared to a GMT of 6,064 EU pre-booster (Day 189) and an approximate 4.7-fold increase from peak GMT (43,905 EU), 14 days following Dose 2 of the primary series.
An approximate 96-fold increase in neutralizing antibodies was shown from a GMT of 63 pre- booster (Day 189) to a GMT of 6,023 post-booster (Day 217) and an approximate 4.1-fold increase from a peak GMT (14 days post-Dose 2) of 1,470.
Study 3 (2019nCoV-501) (South Africa)
Study 3 is an ongoing Phase 2a/b, multicentre, randomised, observer-blinded, placebo-controlled study, the safety and immunogenicity of booster dose was evaluated in healthy in HIV-negative participants 18 to 84 years of age and people living with HIV (PLWH) 18 to 64 years of age in South Africa. PLWH were medically stable (free of opportunistic infections), receiving highly active and stable antiretroviral therapy, and having an HIV-1 viral load of < 1000 copies/mL.
A total of 1,173 participants (PP-IMM Analysis Set) received a booster dose of Novavax COVID-19 vaccine approximately 6 months after completion of the primary series of Novavax COVID-19 vaccine (Day 201).
An approximate 31-fold increase was shown in serum IgG GMT assessed at Day 236 (111,066 EU) from the pre-boost GMT at Day 201 (3,632 EU). An approximate 3.6-fold increase was demonstrated from peak GMT (30,756 EU) at Day 35 following completion of the primary series.
An approximate 52-fold increase in neutralizing antibodies was shown from a GMT of 69 pre-booster (Day 189) to a GMT of 3,600 post-booster (Day 236) and an approximate 5.2-fold increase from a peak GMT (14 days post-Dose 2) of 694.
Elderly population
Novavax COVID-19 vaccine was assessed in individuals 18 years of age and older. The efficacy of Novavax COVID-19 vaccine was consistent between elderly (≥ 65 years) and younger individuals (18 to 64 years).

Immunogenicity data from the Indian studies:
ICMR/SII-COVOVAX Study:
Adult cohort (≥18 years of age):
This is a Phase 2/3, multicenter, randomized, observer-blinded, placebo-controlled study in participants 18 years of age and older in India. A total of 1596 were enrolled in the study and received at least one dose of the study vaccine. Safety was assessed in all 1596 participants while immunogenicity was assessed in 458 participants.
The demographic and baseline characteristics between the groups were comparable. Among 1596 participants, there were 1563 participants (97.9%) between 18 to 59 years of age and remaining 33 (2.1%) were ≥ 60 years of age. Of these 954 were males (59.8%) and 642 were females (40.2%). The median age was 33 years with a range of 18 to 81 years, median BMI was 24.2 kg/m^2. Of these 1596 participants, 198 participants (12.4%) had comorbidities at baseline. Comorbidities included obesity (BMI ≥ 30), diabetes mellitus, hypertension, cardiovascular disorders, dyslipidaemia, hyperthyroidism, hypothyroidism, asthma, chronic obstructive pulmonary disease etc.
Geometric Mean ELISA Units (GMEUs) of IgG antibodies against spike (S) protein were comparable between the groups at baseline - Day 1. GMEUs increased significantly after each dose of vaccine in both the groups and were comparable. There was > 92% seroconversion in both the groups on Day 36 (14 days after second dose) and 78% in both the groups on Day 180 . The immunogenicity data indicates that **COVOVAX™** is comparable in terms of anti-S IgG antibody titers and seroconversion rates to Novavax vaccine (see Tables 10 and 11).

Table 10: Summary of anti-S IgG antibodies in adults

Timepoint	Statistic	COVOVAX™ (N=340)	Novavax vaccine (N=110)
Baseline	N	340	110
	GMEU	2172.3	1708.6
	95% CI	(1799.8, 2621.8)	(1230.7, 2372.2)
21 (+7) days after Dose 1	N	340	110
	GMEU	38350.9	34603.6
	95% CI	(33043.7, 44510.4)	(26002.6, 46049.5)
14 (+7) days after Dose 2	N	338	109
	GMEU	143506.4	152276.9
	95% CI	(133203.2, 154606.7)	(132441.4, 175083.1)
179 (+28) days after Dose 1	N	327	102
	GMEU	34210.6	39189.1
	95% CI	(30945.7, 37820.0)	(31438.0, 48851.3)

Table 11: Summary of proportion of participants with seroconversion for anti-S IgG antibodies in adults

Timepoint	Statistic	COVOVAX™ (N=340)	Novavax vaccine (N=110)
21 (+7) days after Dose 1	N Evaluated	340	110
	Seroconversion, n (%)	281 (82.6)	92 (83.6)
	95% CI	(78.2, 86.5)	(75.4, 90.0)
14 (+7) days after Dose 2	N Evaluated	338	109
	Seroconversion, n (%)	314 (92.9)	105 (96.3)
	95% CI	(89.6, 95.4)	(90.9, 99.0)
179 (+28) days after Dose 1	N Evaluated	327	102
	Seroconversion, n (%)	255 (78.0)	80 (78.4)
	95% CI	(73.1, 82.4)	(69.2, 86.0)

Pediatric cohort (≥ 2 to < 18 years of age):
This is a Phase 2/3, observer-blind, randomized, controlled study in 920 Indian children 2 to 17 years of age, to evaluate the safety and immunogenicity of **COVOVAX™.**

Pediatric cohort (≥12 to <18 years of age):
A total of 460 children of 12 to 17 years of age were enrolled in the study and received at least one dose of the study vaccine. Safety and immunogenicity was assessed in all participants. Of these 241 were males (52.4%) and 219 were females (47.6%). The median age was 14 years with a range of 12 to 17 years, median BMI was 18.7 kg/m^2. None of the participants had any comorbid condition.
GMEUs of anti-S IgG antibodies were comparable between the groups at baseline - Day 1. GMEUs increased substantially after each dose of the vaccine in the **COVOVAX™** group. There was > 98% seroconversion on Day 36 (14 days after the second dose) and > 91% seroconversion on Day 180 (179 days after Dose 1) in the **COVOVAX™** group. The immunogenicity data indicates that **COVOVAX™** is highly immunogenic in the children of ≥ 12 to < 18 years of age (see Tables 12 and 13).

Table 12: Summary of anti-S IgG antibodies in pediatric cohort (≥12 to <18 years of age)

Timepoint	Statistic	COVOVAX™ (N=333)	Placebo (N=108)
Baseline	N	333	108
	GMEU	1664.2	1366.6
	95% CI	(1413.7, 1959.1)	(1033.1, 1807.8)
21 (+7) days after Dose 1	N	332	108
	GMEU	72660.4	1614.6
	95% CI	(63586.3, 83029.4)	(1174.7, 2219.3)
14 (+7) days after Dose 2	N	330	107
	GMEU	170193.6	1480.4
	95% CI	(157429.7, 183992.4)	(1110.1, 1974.3)
179 (+28) days after Dose 1	N	325	67
	GMEU	51961.6	9311.4
	95% CI	(47560.1, 56770.5)	(6388.9, 13570.9)

Table 13: Summary of proportion of participants with seroconversion for anti-S IgG antibodies in pediatric cohort (≥12 to <18 years of age)

Timepoint	Statistic	COVOVAX™ (N=333)	Placebo (N=108)
21 (+7) days after Dose 1	N Evaluated	332	108
	Seroconversion, n (%)	317 (95.5)	4 (3.7)
	95% CI	(92.7, 97.4)	(1.0, 9.2)
14 (+7) days after Dose 2	N Evaluated	330	107
	Seroconversion, n (%)	326 (98.8)	3 (2.8)
	95% CI	(96.9, 99.7)	(0.6, 8.0)
179 (+28) days after Dose 1	N Evaluated	325	67
	Seroconversion, n (%)	298 (91.7)	3 (2.8)
	95% CI	(88.1, 94.5)	(60.9, 83.2)

Pediatric cohort (≥ 2 to <12 years of age):
A total of 460 children of ≥ 2 to < 12 years of age were enrolled in the study and received at least one dose of the study vaccine. Safety and immunogenicity were assessed in all participants. Of these 229 were males (49.8%) and 231 were females (50.2%). The median age was 7 years with a range of 2 to 11 years, median BMI was 14.9 kg/m^2. None of the participants had any comorbid condition.
GMEUs of anti-S IgG antibodies were comparable between the groups at baseline - Day 1. GMEUs increased substantially after each dose of the vaccine in the **COVOVAX™** group. There was 99.1%% seroconversion on Day 36 (14 days after the second dose) and 94.2% seroconversion on Day 180 (179 days after Dose 1) in the COVOVAX™ group. The immunogenicity data indicates that **COVOVAX™** is highly immunogenic in the children of ≥ 2 to < 12 years of age (see Tables 14 and 15).

Table 14: Summary of anti-S IgG antibodies in pediatric cohort (≥ 2 to < 12 years of age)

Timepoint	Statistic	COVOVAX™ (N=326)	Placebo (N=106)
Baseline	N	326	106
	GMEU	1261.1	1346.0
	95% CI	(1048.5, 1516.9)	(953.2, 1900.7)
21 (+7) days after Dose 1	N	325	106
	GMEU	75558.3	1754.8
	95% CI	(65471.0, 87199.9)	(1203.0, 2559.7)
14 (+7) days after Dose 2	N	325	103
	GMEU	214029.6	1626.2
	95% CI	(201610.9, 227213.1)	(1126.0, 2348.8)
179 (+28) days after Dose 1	N	313	97
	GMEU	44882.1	4356.0
	95% CI	(41578.6, 48448.0)	(3181.8, 5963.5)

Table 15: Summary of proportion of participants with seroconversion for anti-S IgG antibodies in pediatric cohort (≥ 2 to < 12 years of age)

Timepoint	Statistic	COVOVAX™ (N=325)	Placebo (N=106)
21 (+7) days after Dose 1	N Evaluated	325	106
	Seroconversion, n (%)	318 (97.8)	6 (5.7)
	95% CI	(95.6, 99.1)	(2.1, 11.9)
14 (+7) days after Dose 2	N Evaluated	325	103
	Seroconversion, n (%)	322 (99.1)	8 (7.8)
	95% CI	(97.3, 99.8)	(3.4, 14.7)
179 (+28) days after Dose 1	N Evaluated	313	97
	Seroconversion, n (%)	295 (94.2)	42 (43.3)
	95% CI	(91.1, 96.6)	(33.3, 53.7)

COVOVAX-Booster study:
This is an ongoing Phase 3, observer-blinded, randomised, active controlled study in adults ≥ 18 years of age in India who had already received primary vaccination against COVID-19 at least 6 months ago (6 months / 180 days from the second dose). A total of 186 participants each in Covishield Prime cohort and Covaxin Prime cohort received study vaccines. The demographic and baseline characteristics between the two groups in both the cohorts were comparable.
Baseline GMEUs of anti-S IgG were comparable between the groups at baseline - Day 1. At 28 days after the COVOVAX booster dose, there was increase in the titers of anti-S IgG antibodies with 3.9 fold-rise (95% CI 3.4, 4.5) and 7.4 fold-rise (95% CI 5.9, 9.1) from the baseline in the Covishield and Covaxin Prime cohort respectively. COVOVAX as a booster dose was non-inferior to both Covishield and Covaxin in terms of anti-S IgG and neutralizing antibodies in adults. GMTs of both anti-S IgG and neutralizing antibodies of COVOVAX booster were around 2 times higher than the Covishield booster and more than 5 times higher than the Covaxin booster.

5.2 Pharmacokinetic properties
Not applicable.

5.3 Preclinical safety data
Non-clinical data reveal no special hazards for humans based on conventional studies of repeat dose toxicity, local tolerance and reproductive and developmental toxicity.
Genotoxicity and Carcinogenicity:
In vitro genotoxicity studies were conducted with the novel Matrix-M1 adjuvant and the adjuvant was shown to be non-genotoxic. Carcinogenicity studies were not performed. Carcinogenicity is not expected.
Reproductive toxicity:
A developmental and reproductive toxicity study was performed in female rats administered four intramuscular doses (two prior to mating; two during gestation) of 5 µg SARS-CoV-2 rS protein (approximately 200-fold excess relative to the human dose of 5 µg on a weight-adjusted basis) with 10 µg Matrix-M1 adjuvant (approximately 40-fold excess relative to the human dose of 50 µg on a weight-adjusted basis). No vaccine-related adverse effects on fertility, pregnancy/lactation, or development of the embryo/fetus and offspring through post-natal Day 21 were observed.

6 PHARMACEUTICAL PARTICULARS
6.1 List of Excipients
The excipients used in the manufacturing of **COVOVAX™** are listed below:
Adjuvant Matrix-M1
Disodium hydrogen phosphate heptahydrate
Sodium dihydrogen phosphate monohydrate
Sodium chloride
Polysorbate 80
Water for Injections

6.2 Incompatibilities
In the absence of compatibility studies, this vaccine must not be mixed with other medicinal products, vaccines or diluted.

6.3 Shelf-life
The expiry date of vaccine is indicated on the label and packaging.
Once opened (first needle puncture) multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2°C and +25°C. All opened (punctured) multidose vials of **COVOVAX™** should be discarded at the end of immunization session or six hours after the first needle puncture, whichever comes first.

6.4 Special Precautions for Storage
Store in a refrigerator (+2°C to +8°C). Do not freeze. Keep vials in outer carton to protect from light.
Discard if vaccine has been frozen.
Opened multidose vial (after the first use)
For storage conditions after the first opening of the medicinal product, see section 6.3.

6.5 Nature and Contents of Container
COVOVAX™ is supplied as ready to use liquid in rubber-stoppered single and multidose vial in below listed presentations
1 dose - 0.5 ml per vial
2 dose - 1 ml per vial
10 doses - 5 ml per vial
20 doses - 10 ml per vial
Not all pack sizes may be marketed.

6.6 Instructions for Use, Handling and Disposal
Administration:
COVOVAX™ is a Colourless to slightly yellow, clear to mildly opalescent, free to practically free from visible particles. The vaccine should be 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. 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 the first opening, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2°C and +25°C. 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
Any unused vaccine or waste material should be disposed off in accordance with local requirements.

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Manufactured by:
SERUM INSTITUTE OF INDIA PVT. LTD.
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(TM) Trademark under registration

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