SARS-CoV-2 rS Protein Nanoparticle vaccine [Recombinant]

COVOVAX

1. NAME OF THE MEDICINAL PRODUCT

COVOVAX
(SARS-CoV-2 rS Protein Nanoparticle vaccine [Recombinant])

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

These are single dose vials.
One single dose vial contains 1 dose of 0.5 mL, [see Nature and Contents of Container]
One dose (0.5 mL) contains 5 micrograms of the SARS-CoV-2 (Omicron XBB.1.5) spike protein* and is adjuvanted with Matrix-M.
Adjuvant Matrix-M containing per 0.5 mL dose: Fraction-A (42.5 micrograms) and Fraction-C (7.5 micrograms) of Quillaja saponaria Molina extract.
*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 full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Dispersion for injection.
The dispersion is colourless to slightly yellow, clear to mildly opalescent (pH 7.2)

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

COVOVAX (also referred as COVID-19 Vaccine XBB.1.5 throughout this document) is indicated for active immunization to prevent COVID-19 caused by SARS- CoV-2 in individuals 12 years of age and older.

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

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Primary vaccination series

COVID-19 Vaccine XBB.1.5 is administered as a course of two doses of 0.5 mL each. It is recommended to administer the second dose 3 weeks after the first dose.

Booster Dose

A booster dose of COVID-19 Vaccine XBB.1.5 (0.5 mL) may be administered intramuscularly approximately 3 months after the primary series of COVID-19 Vaccine XBB.1.5 in individuals 12 years of age and older (homologous booster dose). COVID-19 Vaccine XBB.1.5 may also be given as a booster dose in individuals 18 years of age and older following a primary series with other COVID-19 vaccines (heterologous booster dose). The dosing interval for the heterologous booster dose is the same as that authorised for a booster dose of the vaccine used for primary vaccination.

Paediatric population

The safety and immunogenicity of COVID-19 Vaccine (recombinant, adjuvanted) has been established in children aged 12 through 17 years.
No dose adjustment is required for the approved age group.

Elderly population

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

Method of administration

COVID-19 Vaccine XBB.1.5 is for intramuscular injection only, preferably into the deltoid muscle of the upper arm.
Do not inject the vaccine intravascularly, subcutaneously, or intradermally.
The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products. For precautions to be taken before administering the vaccine, see section 6.6.
For instructions on handling and disposal of the vaccine, 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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported with COVID-19 vaccine (Original, Wuhan strain). 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. The vaccine should not be given to those who have experienced anaphylaxis to a prior dose of COVID-19 vaccine (Original, Wuhan strain).

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with COVID-19 vaccine (Original, Wuhan strain). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days.
Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.
Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis.
Vaccinees (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.
Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

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 following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy, safety, and immunogenicity of the vaccine has been assessed in a limited number of immunocompromised individuals. The efficacy of COVID-19 Vaccine XBB.1.5 may be lower in immunosuppressed individuals.

Duration of protection

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

Limitations of vaccine effectiveness

Individuals may not be fully protected until 7 days after their second dose. As with all vaccines, vaccination with COVID-19 Vaccine XBB.1.5 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 dose, that is to say, essentially 'potassium-free'.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Co-administration of COVID-19 vaccine (Original, Wuhan strain) with inactivated influenza vaccines has been evaluated in a limited number of participants in an exploratory clinical trial sub-study, see section 4.8 and section 5.1.
The binding antibody response to SARS-CoV-2 was lower when COVID-19 vaccine (Original, Wuhan strain) was given concomitantly with inactivated influenza vaccine. The clinical significance of this is unknown.
Concomitant administration of COVID-19 Vaccine XBB.1.5 with other vaccines has not been studied.

4.6. FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There is limited experience with use of COVID-19 vaccine (Original, Wuhan strain) 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 6.1.
Administration of COVID-19 Vaccine XBB.1.5 in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breast-feeding

It is unknown whether COVID-19 Vaccine XBB.1.5 is excreted in human milk.
No effects on the breast-fed newborn/infant are anticipated since the systemic exposure of the breast- feeding woman to COVID-19 Vaccine XBB.1.5 is negligible.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, see section 6.1.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

COVID-19 Vaccine XBB.1.5 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8. UNDESIRABLE EFFECTS

The safety of COVID-19 Vaccine (recombinant, adjuvanted) XBB.1.5 is inferred from the safety data of the COVID-19 Vaccine (Original, Wuhan strain) and investigational vaccines targeting the Omicron BA.1 variant and the Omicron BA.5 variant.

COVID-19 vaccine (Original, Wuhan strain)

Summary of the safety profile after primary series

Participants 18 years of age and older after two primary series:

The safety of COVID-19 vaccine (Original, Wuhan strain) 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 aged 18 years and older received at least one dose of the two-dose primary series of COVID-19 vaccine (Original, Wuhan strain) (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 aged 18 years and older enrolled in the two phase 3 studies who received any dose of COVID-19 vaccine (Original, Wuhan strain) (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 COVID-19 vaccine (Original, Wuhan strain) in adolescents was evaluated in an interim analysis of the paediatric expansion portion of an ongoing Phase 3 multicentre, randomised, observer-blinded, placebo- controlled study (Study 2019nCoV-301).
Safety data were 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 COVID-19 vaccine (Original, Wuhan strain) (n=1,487) or placebo (n=745).
Demographic characteristics were similar among participants who received COVID-19 vaccine (Original, Wuhan strain) 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.

Summary of the safety profile after booster dose

Participants 18 years of age and older

The safety and immunogenicity of a booster dose of COVID-19 vaccine (Original, Wuhan strain) 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 COVID-19 vaccine (Original, Wuhan strain) (0.5 mL 3 weeks apart) as the primary vaccination series. A subset of 105 participants received a booster dose of COVID-19 vaccine (Original, Wuhan strain) 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%), headache (46%), joint pain (29%), and fever (17%) with a median duration of 1 to 3 days following vaccination.
In a second ongoing Phase 2a/b randomized, placebo-controlled, observer-blinded clinical study conducted in South Africa (Study 2019nCoV-501), the immunogenicity and safety of a booster dose of COVID-19 vaccine (Original, Wuhan strain) was evaluated in healthy HIV-negative participants 18 to 84 years of age (Cohort 1) and medically stable people living with HIV (PLWH) 18 to 64 years of age (Cohort 2). Overall, 1,898 participants (Safety Analysis Set) received a booster dose of COVID-19 vaccine (Original, Wuhan strain) approximately 6 months after receiving the second dose of the two-dose primary series. Solicited adverse reactions were not collected following the booster dose.

Study 2019nCoV-301 Booster Data

The safety and immunogenicity of a booster dose of COVID-19 vaccine (Original, Wuhan strain) was evaluated in an ongoing Phase 3, multicenter, randomized, observer-blinded, placebo-controlled study (Study 2019nCoV-301). Overall, 12,777 participants received a booster dose of the vaccine at least 6 months after the two-dose primary series (median of 11 months between completion of primary series and booster dose). Of the 12,777 participants who received a booster dose, 39 participants did not receive COVID-19 vaccine (Original, Wuhan strain) for all three doses. The safety analyses included evaluation of solicited local and systemic adverse reactions within 7 days after a booster dose for participants who completed the electronic diary (n=10,137).
The most frequent solicited adverse reactions were injection site pain/tenderness (78.5%), fatigue/malaise (58.2%), muscle pain (51.4%), headache (45.4%), and joint pain (26.1%).

Adolescents 12 through 17 years of age

The safety of a booster dose of COVID-19 vaccine (Original, Wuhan strain) was evaluated in an interim analysis of an ongoing Phase 3 study (Study 2019nCoV-301). A total of 2,122 participants received two doses of COVID-19 vaccine (Original, Wuhan strain) (0.5 mL 3 weeks apart) as the primary vaccination series. A total of 1,499 participants received a booster dose approximately 9 months after receiving Dose 2 of the primary series. A subset of 220 participants who received the booster dose were evaluated for solicited adverse reactions within 7 days after the booster dose (Ad Hoc Booster Safety Analysis Set).
The most frequent solicited adverse reactions were injection site tenderness (71.6%), headache (68.4%), fatigue (65.8%), pain (63.7%), muscle pain (61.6%), malaise (46.8%), and nausea/vomiting (26.3%) with a median duration of 1 to 2 days following vaccination. No new safety concerns from the time of the booster dose administration through 28 days after administration were noted among participants.

Tabulated list of adverse reactions

Adverse reactions observed during clinical studies are listed below according to the following frequency categories:
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).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions from COVID-19 vaccine (Original, Wuhan strain) clinical trials and post-Authorisation experience in individuals 12 years of age and older

System Organ Class Preferred Term	Frequency[d] (category)
Blood and lymphatic disorders	
Lymphadenopathy	Uncommon
Nervous system disorders	
Headache	Very common
Gastrointestinal disorders	
Nausea or vomiting[a]	Very common
Skin and subcutaneous disorders	
Rash	Uncommon
Erythema	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	
Myalgia[a]	Very common
Arthralgia[a]	Very common
General disorders and administrative site conditions	
Injection site tenderness[a]	Very common
Injection site pain[a]	Very common
Fatigue[a]	Very common
Malaise[a,b]	Very common
Injection site redness[c]	Common
Injection site swelling	Common
Pyrexia	Common
Chills	Uncommon
Pain in extremity	Common
Injection site pruritus	Uncommon

[a] Higher frequency 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)
[d] Adverse reactions observed during clinical studies are listed below according to the following frequency categories: 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).

COVID-19 Vaccine XBB.1.5 (Omicron-adapted vaccine)

Study 2019nCoV-311 Booster Data

Part 1

The safety of COVID-19 vaccine (Original, Wuhan strain), the monovalent vaccine (Omicron BA.1) and the bivalent vaccine (Original and Omicron BA.1) administered as a booster dose to individuals 18 through 64 years of age, previously vaccinated with three doses of an authorized or approved mRNA COVID-19 vaccine was assessed in a randomized, observer blind study (NCT05372588, in Australia).
The safety analysis set included 274 participants in the COVID-19 vaccine (Original, Wuhan strain) group, 286 participants in the monovalent vaccine (Omicron BA.1) group, and 269 participants in the bivalent vaccine (Original and Omicron BA.1) group. The median time since the last COVID-19 vaccination was 180.0 days. Local and systemic adverse reactions were solicited within 7 days following vaccination with COVID-19 vaccine (Original, Wuhan strain), the monovalent vaccine (Omicron BA.1), or the bivalent vaccine (Original and Omicron BA.1) using an electronic diary.
The most frequent solicited adverse reactions in those receiving Monovalent Vaccine (Omicron BA.1) were injection site pain/tenderness (69.3%), fatigue/malaise (44.9%), muscle pain (25.1%), headache (37.5%), and joint pain (9.5%). A comparable safety profile was seen across all vaccine groups.

Part 2

The safety of COVID-19 vaccine (Original, Wuhan strain), the monovalent vaccine (Omicron BA.5), and the bivalent vaccine (Original and Omicron BA.5) administered as a booster dose to individuals 18 years of age and older previously vaccinated with three or more doses of an authorized or approved mRNA COVID-19 vaccine was assessed in a randomized, observer blind study (NCT05372588, Part 2 in Australia).
The safety analysis set included 251 participants in the COVID-19 vaccine (Original, Wuhan strain) group, 254 participants in the monovalent vaccine (Omicron BA.5) group and 259 participants in the bivalent vaccine (Original and Omicron BA.5) group. The median time since the last COVID-19 vaccination was 352.5 days. Local and systemic adverse reactions were solicited within 7 days following vaccination with COVID-19 vaccine (Original, Wuhan strain), the monovalent vaccine (Omicron BA.5), or the bivalent vaccine (Original and Omicron BA.5) using an electronic diary.
The most frequent solicited adverse reactions in those receiving Monovalent Vaccine (Omicron BA.5) were injection site pain/tenderness (60.7%), fatigue/malaise (42.1%), muscle pain (23.4%), headache (29.0%), nausea/vomiting (7.5%) and joint pain (7.1%). A comparable safety profile was seen across all vaccine groups.

Study 2019nCoV-313

The safety of the of a booster dose of NVX-CoV2601 (Omicron XBB.1.5 subvariant vaccine) was evaluated in participants ≥ 18 years of age who previously received ≥ 3 doses of the Moderna and/or Pfizer/BioNTech prototype monovalent and/or BA.4/5 containing bivalent mRNA COVID-19 vaccines administered ≥ 90 days prior to study vaccination (Part 1) and in baseline SARS-CoV-2 seropositive COVID-19 vaccine naïve participants ≥ 18 years of age (Part 2) in the US and its territories. In Part 1 and Part 2 of the study, participants received booster vaccination on Day 0 and will be followed for immunogenicity and safety data collection through Day 180 with interim analyses planned at Day 28. The safety data from part 1 of the study in 332 participants is summarized below:
Solicited local injection site AEs were reported in 189 (56.9%) participants within 7 days following booster vaccination with NVX-CoV2601, with higher frequencies in participants 18 to 54 years of age (64.2%) than in participants ≥ 55 years of age (48.7%). Pain/tenderness were the most frequent (incidence > 20%) solicited local injection site AEs.
Fatigue/malaise, muscle pain, and headache were the most frequent (incidence > 20%) solicited systemic AEs. Unsolicited AEs within 28 days of booster vaccination with NVX-CoV2601 were reported in less than 10% of participants, with most unsolicited AEs being mild or moderate in severity and not related to study vaccine. SAEs were infrequent, occurring in 2 (0.6%) participants, none were related to study vaccine.
The incidence of solicited local injection site and systemic reactogenicity with NVX-CoV2601 was consistent with the reactogenicity seen in previous studies with NVX-CoV2373. These data show that there is no change in the safety profile of SARS-CoV-2 rS protein subunit vaccine with XBB.1.5 strain change.

COV-BOOST

Additionally, the safety of a COVID-19 vaccine (Original, Wuhan strain) booster dose in individuals who completed a primary vaccination with another authorized or approved COVID-19 vaccine (heterologous booster dose) is inferred from the report of an independent, multicentre, randomized, controlled, Phase 2, trial conducted in the United Kingdom (ISRCTN 73765130). This study was conducted in adults aged 30 years and older with no history of laboratory-confirmed SARS-CoV-2 infection. One study group (n=114 participants; median age 63 years) received COVID-19 vaccine (Original, Wuhan strain) administered at least 84 days (median 105 days) after completion of the Pfizer-BioNTech COVID-19 Vaccine primary series. Reported adverse reactions through 28 days following a COVID-19 vaccine (Original, Wuhan strain) booster dose did not identify any new safety concerns, as compared with adverse reactions reported following two doses of COVID-19 vaccine (Original, Wuhan strain) given as a primary series.

Overall summary of the safety profile from the Indian studies:

ICMR/SII-COVOVAX Study:

Adult cohort (≥ 18 years of age):
COVOVAX (Original, Wuhan strain) 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 (Wuhan strain) 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 the 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 (Original, Wuhan strain) 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 was 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 (Original, Wuhan strain).

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 (Original, Wuhan strain) was well tolerated with an acceptable safety profile. Pain (37%) and tenderness (11.6%) were the most frequent solicited local adverse events. Fever (22.5%), headache (19.1%), fatigue (14.5%), and malaise (9.5%) 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 (Original, Wuhan strain) 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 (Original, Wuhan strain) and 115 Placebo) and 445 received the second dose of study vaccine (333 COVOVAX (Wuhan strain) and 112 Placebo). Demographic characteristics were generally similar among participants across both the groups.
COVOVAX (Original, Wuhan strain) 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 (Original, Wuhan strain) 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 was a 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. Headache (14.1%), malaise (13%), and fatigue (12%) 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: Vaccine, protein subunit, ATC code: J07BN04

Mechanism of Action

COVID-19 Vaccine XBB.1.5 is composed of purified full-length SARS-CoV-2 Omicron XBB.1.5 recombinant spike (S) protein that is stabilized in its prefusion conformation. The addition of the saponin-based Matrix-M 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 neutralizing antibodies, which may contribute to protection against COVID-19.

COVID-19 vaccine (Original, Wuhan strain)

Clinical efficacy

Primary series

The clinical efficacy, safety, and immunogenicity of COVID-19 vaccine (Original, Wuhan strain) 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, and a Phase 2a/b study, Study 3, conducted in South Africa.
The effectiveness of COVID-19 Vaccine (recombinant, adjuvanted) XBB.1.5 for individuals 12 years of age and older is inferred from studies which evaluated the primary series and booster vaccination with COVID-19 vaccine (Original, Wuhan strain) and supported by a study of a booster dose of an investigational vaccines targeting the Omicron BA.5 variant of SARS-CoV-2 in individuals 18 years of age and older, and by a study of a booster dose of an investigational vaccine targeting the Omicron BA.1 variant of SARS-CoV-2 in individuals 18 to 64 years of age.

Study 1 (2019nCoV-301)

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 the United States and Mexico, and a paediatric 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 COVID-19 vaccine (Original, Wuhan strain) 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 COVID-19 vaccine (Original, Wuhan strain) (n = 17,312) or placebo (n = 8,140), received two doses (Dose 1 on day 0; Dose 2 at day 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 COVID-19 vaccine (Original, Wuhan strain) and those who received placebo.
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	COVID 19 vaccine (Original, Wuhan strain)			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)	----	----
Severe	----	0	----	----	4 (< 0.1)	----	----

[1] VE evaluated in participants without major protocol deviations, 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 results reflect enrolment that occurred during the time period when strains classified as Variants of Concern or Variants of Interest were predominantly circulating in the two countries (US and Mexico) where the study was conducted.
Vaccine efficacy of COVID-19 vaccine (Original, Wuhan strain) to prevent the onset of COVID-19 from seven days after Dose 2 was 90.4% (95% CI 82.9,94.6). No cases of severe COVID-19 were reported in the 17,312 COVID-19 vaccine (Original, Wuhan strain) participants compared with 4 cases of severe COVID-19 reported in the 8,140 placebo recipients in the PP-EFF analysis set.

Efficacy in adolescents 12 through 17 years of age

The primary endpoint of effectiveness defined by non-inferior immunogenicity of COVID-19 vaccine (Original, Wuhan strain) in adolescent participants 12 through 17 years of age occurred in the United States in the ongoing paediatric expansion portion of the Phase 3 multicentre, randomised, observer-blinded, placebo-controlled 2019nCoV-301 study.
A total of 1,799 participants, assigned in a 2:1 ratio to receive two doses of COVID-19 vaccine (Original, Wuhan strain) (n=1,205) or placebo (n=594) by intramuscular injection 21 days apart, represented the Per Protocol 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 (COVID-19 vaccine (Original, Wuhan strain), n=6 [0.5%]; placebo, n=14 [2.4%]) 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 from which 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]), point estimate of the ratio of GMTs ≥ 0.82; and the lower bound of the two-sided 95% CI for difference of seroconversion rates (SCRs) (SCR 12 through 17 years minus SCR 18 through 25 years) > -10%.) was met. GMTs are as presented in Table 87.

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

Assay	Timepoint	Paediatric Expansion (12 through 17 Years) N=390	Adult Main Study (18 through 25 Years) N=416	12 through 17 Years versus 18 through 25 Years
		GMT 95% CI[2]	GMT 95% CI[2]	GMR 95% CI[2]
Microneutralisation (1/dilution)	Day 35 (14 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 coronavirus 2.
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 through 25 years) with non-missing neutralizing antibodies result
n2 = number of participants in pediatric expansion (12 through 17 years) with non-missing neutralizing antibodies result

Study 2 (2019nCoV-302)
Study 2 was a 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 COVID-19 vaccine (Original, Wuhan strain) or placebo.
The primary efficacy analysis set (PP-EFF) included 14,039 participants who received either COVID-19 vaccine (Original, Wuhan strain) (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 COVID-19 vaccine (Original, Wuhan strain) 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	COVID-19 vaccine (Original, Wuhan strain)			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 COVID-19 vaccine (Original, Wuhan strain) 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 COVID-19 vaccine (Original, Wuhan strain) 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.1.1.7 (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 COVID-19 vaccine (Original, Wuhan strain) 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 COVID-19 vaccine (Original, Wuhan strain) and 214 received placebo.
Demographic and baseline characteristics were balanced amongst participants who received COVID-19 vaccine (Original, Wuhan strain) 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 COVID-19 vaccine (Original, Wuhan strain) 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).
Booster dose (Original Wuhan strain and Omicron BA.1 and BA.5 variants)
Immunogenicity in participants 18 years of age and older
Study 2019nCoV-101, Part 2
The safety and immunogenicity of a booster dose of COVID-19 vaccine (Original, Wuhan strain) 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 255 participants received two doses of COVID-19 vaccine (Original, Wuhan strain) (0.5 mL, 5 micrograms 3 weeks apart) as the primary vaccination series. Within all participants, a subset of 105 participants received a booster dose of COVID-19 vaccine (Original, Wuhan strain) approximately 6 months after receiving Dose 2 of the primary series.
A single booster dose of COVID-19 vaccine (Original, Wuhan strain) induced a 31.2-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 200,243 EU compared to a GMT of 6,151 EU pre-booster (Day 189) A GMR of 4.7 from peak GMT (42,173 EU), 14 days following Dose 2 of the primary series was demonstrated.
A 79.6-fold increase in neutralizing antibodies was shown from a GMT of 68 pre-booster (Day 189) to a GMT of 5542 post-booster (Day 217). A GMR of 4.0 from a peak GMT (14 days post-Dose 2) of 15461.
Study 2019nCoV-501
In a Phase 2a/b, multicenter, randomized, observer-blinded, placebo-controlled study, the safety and immunogenicity of booster dose was evaluated in healthy HIV-negative adult participants 18 to 84 years of age and people living with HIV (PLWH) 18 to 64 years of age who were seronegative to SARS-CoV-2 at baseline. 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 1804 participants (PP-IMM Analysis Set) received a booster dose of COVID-19 vaccine (Original, Wuhan strain) approximately 6 months after completion of the primary series of COVID-19 vaccine (Original, Wuhan strain) (Day 201).
A 17.1-fold increase was shown in serum IgG GMT assessed at Day 236 (114,679 EU) from the pre-boost GMT at Day 201 (5,950 EU). A GMR of 2.2 was demonstrated from peak GMT (52,023 EU) at Day 35 following completion of the primary series.
A 20.6-fold increase in neutralizing antibodies was shown from a GMT of 146 pre-booster (Day 201) to a GMT of 3,726 post-booster (Day 236). A GMR of 2.7 was demonstrated from a peak GMT (14 days post-Dose 2) of 1,352
Study 2019nCoV-301
In the open-label booster phase of Study 2019nCoV-301, participants 18 years of age and older received a single booster dose of the COVID-19 vaccine (Original, Wuhan strain) at least 6 months after completion of the primary series. A subset of 226 participants were included in the per-protocol immunogenicity (PP-IMM) analysis set as they did not have serologic or virologic evidence of SARS-CoV-2 infection up to 28 days post booster dose.
Prespecified immunogenicity non-inferiority analyses included an assessment of MN_{50} geometric mean titer (GMT) ratio and difference in seroconversion rates. Seroconversion for a participant was defined as achieving a 4-fold rise in MN_{50} from baseline (before the booster dose and before the first dose of the primary series).
The analysis of the GMT ratio of MN_{50} following the booster dose compared to the primary series met the non-inferiority criteria for a booster response (lower limit of the 95% CI > 0.67) and point estimate > 0.83.
The analysis of the difference in seroconversion rates following the booster dose compared to the primary series met the non-inferiority criteria for a booster response (lower limit of the 95% CI > -10%).
In addition, a single booster dose of the Novavax COVID-19 Vaccine, (recombinant, adjuvanted) elicited a robust immune response (serum IgG antibody) against the Omicron BA.1 variant at 28 days after booster vaccination that were higher than that reported at 14 days after primary series vaccination in the same participants.
Additionally, in Study 301, approximately 6 months after completion of the third dose (first booster) with COVID-19 vaccine (Original, Wuhan strain), 356 participants at selected sites received a fourth dose (second booster) of COVID-19 vaccine (Original, Wuhan strain). Dosing was initiated on 19 September 2022, with enrolment completed on 01 October 2022. Immunogenicity data were collected from 331 participants immediately prior to administering the fourth dose and at 28 days after vaccination based on data cut-off date of 08 November 2022. Safety data were assessed in 356 participants from the time of administration of the second booster dose through the data cut-off date of 08 November 2022.
Study 2019nCoV-311
Study 2019nCoV-311 is a 2-part, Phase 3, randomized, observer-blinded study conducted to evaluate the safety and immunogenicity of COVID-19 vaccine (Original, Wuhan strain) in adults in Australia.
In Part 1, a subgroup of participants 18 to 64 years of age who previously received 3 doses of the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine, received one of the following as a booster dose: COVID-19 vaccine (Original, Wuhan strain) or monovalent vaccine (Omicron BA.1). The booster doses were administered at a median of 182 and 177 days after the last vaccination, respectively. Neutralizing antibody titers for the Omicron BA.1 virus, measured by a microneutralization assay [MN50], were evaluated at 14 days after vaccination. Participants included in the day 14 per protocol analysis set population (n=240) had no serologic or virologic evidence of SARS-CoV-2 infection prior to the booster dose.
Prespecified immunogenicity analyses included an assessment of MN50 GMT ratio and difference in seroresponse rates. Seroresponse rate was defined as the percentage of participants achieving a 4-fold rise in MN50 from baseline (before the first dose of the study vaccine).
The analysis of the GMT ratio following the booster dose with monovalent vaccine (Omicron BA.1) compared to the booster dose with COVID-19 vaccine (Original, Wuhan strain) met the superiority criterion for success (lower limit of the 95% CI > 1.0).
The lower limit of the two-sided 95% CI for the difference in seroresponse rates (percentage) was 10.3%, which met the non-inferiority criterion for success (lower limit of 95% CI for the percentage difference of > -5%).
In sensitivity analyses using a per protocol analysis set that did not exclude participants with serologic evidence of SARS-CoV-2 infection (PP2 Analysis Subset, n= 491), neutralizing antibody responses against the Omicron BA.1 virus induced by the monovalent vaccine (Omicron BA.1) were compared with neutralizing antibody responses against the Omicron BA.1 virus induced by the COVID-19 vaccine (Original, Wuhan strain) 14 days after study vaccination.
The GMTs were 318.2 (95% CI: 269.8, 375.3) in the monovalent vaccine (Omicron BA.1) group (n= 247) and 218.1 (95% CI: 186.0, 255.7) in the COVID-19 vaccine (Original, Wuhan strain) group (n= 244), resulting in an estimated GMT ratio of the monovalent vaccine (Omicron BA.1) versus the COVID-19 vaccine (Original, Wuhan strain) of 1.5 (95% CI: 1.36, 1.77).
The seroresponse rates (percentage) were 54.3% in the monovalent vaccine (Omicron BA.1) group and 32.0% in the COVID-19 vaccine (Original, Wuhan strain) group, resulting in a difference in seroresponse rates (percentage) of 22.3% (95% CIs: 13.6%, 30.6%).
In Part 2, a subgroup of participants 18 years of age and older who previously received at least 3 doses of the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine, received one of the following as a booster dose: COVID-19 vaccine (Original, Wuhan strain) or monovalent vaccine (Omicron BA.5). The booster doses were administered a median of 389 and 328 days after the last vaccination, respectively. Neutralizing antibody titers against a pseudovirus expressing the SARS-CoV-2 Spike protein from the Omicron BA.5 virus, measured by pseudovirus neutralization assay [ID50], were evaluated at 28 days after vaccination. Participants included in the day 28 per protocol analysis set population (n=462) had no virologic evidence of SARS-CoV-2 infection at time of the booster dose.
Exploratory immunogenicity analyses included an assessment of the ID50 GMT ratio and difference in seroresponse rates. Seroresponse rate was defined as the percentage of participants achieving a 4-fold rise in ID50 from baseline (before the first dose of the study vaccine).
The GMT ratio following the booster dose with monovalent vaccine (Omicron BA.5) compared with the booster dose with COVID-19 vaccine (Original, Wuhan strain) was 2.5 (two-sided 95% confidence interval: 2.10, 2.94).
The difference in seroresponse rates (percentage) between the booster dose with monovalent vaccine (Omicron BA.5) and the booster dose with COVID-19 vaccine (Original, Wuhan strain) was 33.2% (two-sided 95% confidence interval: 25.4%, 40.7%).
Study 2019nCoV-313
Study 2019nCoV-313 is a 2-part, Phase 2/3 open-label, single-arm study which evaluated the safety and immunogenicity of a booster dose of NVX-CoV2601 in previously messenger ribonucleic acid (mRNA) COVID-19 vaccinated adult participants ≥ 18 years of age (Part 1) and in baseline SARS-CoV-2 seropositive COVID-19 vaccine naïve participants ≥ 18 years of age (Part 2) in the United States (USA) and its territories.
In part 1, a total of 332 participants were enrolled in the study in the US and its territories, with 329 (99.1%) in follow up. NVX-CoV2601 induced a superior response in adjusted GMT (ID50) versus NVX-CoV2373 against the Omicron XBB.1.5 subvariant pseudovirus (905.9 vs 156.6, respectively) with a GMTR of 5.8 (95% CI: 4.85, 6.91). The NVX-CoV2601 and historical control NVX-CoV2373 GMFR between baseline to Day 28 was 7.9 (95% CI: 6.8, 9.2) and 1.5 (95% CI: 1.3,1.6), respectively (Table 11). NVX-CoV2601 induced a non-inferior seroresponse rate (SRR) against the Omicron XBB.1.5 subvariant virus versus the historical control Novavax vaccine NVX-CoV2373 (64.3% vs 7.0%, respectively) at Day 28, with a difference in SRRs of 57.2% (95% CI: 50.5, 63.2) (Table 10).

Table 10: Summary of Serum Neutralizing Antibody Titers Against the Omicron XBB.1.5 Subvariant Pseudovirus Following Booster Vaccination with NVX-CoV2601 (per protocol population)

Time point	Parameters	NVX-CoV2601 Booster N = 309	Historical Control NVX-CoV2373 Booster N = 227
Day 0 (baseline)	GMT (ID_{50}) (95% CI)	120.8 (101.5, 143.8)	100.0 (80.8, 123.8)
Day 28	Adjusted GMT (ID_{50}) (95% CI)	905.9 (807.1, 1016.8)	156.6 (137.0, 179.0)
	GMFR referencing Day 0 (95% CI)	7.9 (6.8, 9.2)	1.5 (1.3, 1.6)
	SRR ≥ 4-fold increase, n2/n1 (%)	196/305 (64.3)	16/227 (7.0)
	95% CI	58.6, 69.6	4.1, 11.2
Comparison between groups		**NVX-CoV2601 vs NVX-CoV2373**	
GMTR (95% CI)		5.8 (4.85, 6.91)	
Difference in SRR (95% CI)		57.2 (50.5, 63.2)	

NVX-CoV2601 booster was demonstrated superiority against the historical control NVX-CoV2373 booster in terms of GMT ratio of neutralizing antibodies against the Omicron XBB.1.5 subvariant pseudovirus and non-inferiority for the difference in SRRs at Day 28.
Booster dose in Adolescents 12 through 17 years of age
The safety and immunogenicity of a booster dose of COVID-19 vaccine (Original, Wuhan strain) was evaluated in a Phase 3, multinational, multicenter, randomized, observer-blinded, placebo-controlled Pediatric Expansion study involving 220 adolescents 12 through 17 years of age conducted in the United States. Of these, 110 participants received a booster dose after first receiving placebo during the initial (precrossover) vaccination period followed by active vaccination during the blinded crossover period [Cohort 1] and 110 who received a booster dose after first receiving active vaccination during the initial (precrossover) vaccination period followed by placebo during the blinded crossover period [Cohort 2]) from 58 sites in the United States. All adolescent participants aged 12 through 17 years of age were seronegative to SARS-CoV-2 at baseline.
The study assessed the immune response (neutralizing antibody against SARS-CoV-2 wild-type virus, serum immunoglobulin G [IgG] antibody to SARS-CoV-2 S protein immediately prior to and at 28 days after administration of a booster dose of COVID-19 vaccine (Original, Wuhan strain) and evaluated the overall safety profile of COVID-19 vaccine (Original, Wuhan strain) through 28 days after the booster dose in 220 randomly selected adolescent participants aged 12 through 17 years of age.
A total of 2,122 participants received two doses of COVID-19 vaccine (Original, Wuhan strain) (0.5 mL, 5 micrograms 3 weeks apart) as the primary vaccination series. A total of 1,499 participants received a booster dose of COVID-19 vaccine (Original, Wuhan strain) approximately 9 months after completing the primary vaccination series, and of those 220 were selected for immunogenicity analysis. This resulted in 53 participants eligible to be analyzed as part of the primary endpoint.
A single booster dose of COVID-19 vaccine (Original, Wuhan strain) induced an approximate 34.2-fold increase in the immune response against the Wuhan (ancestral) strain 28 days after receipt of the dose with a serum IgG geometric mean ELISA unit (GMEU) of 388,263.3 EU/mL compared to a GMEU of 11,339.4 EU/mL pre-booster and an approximate 2.5-fold increase from peak GMEU (156,286.4 EU/mL), 14 days following Dose 2 of the primary series.
An approximate 27.7-fold increase in neutralizing antibodies was shown from a GMT of 426.7 pre-booster to a GMT of 11824.4 post-booster and an approximate 2.7-fold increase from a peak GMT (14 days post-Dose 2) of 4434.0.
A single booster dose of COVID-19 vaccine (Original, Wuhan strain) administered to adolescent participants 12 through 17 years of age elicited robust immune responses (neutralizing antibody (Mn_{50}), serum IgG antibody, and hACE2 receptor binding inhibition) against the SARS-CoV-2 wild type virus (ancestral Wuhan strain) at 28 days after the booster dose of COVID-19 vaccine (Original, Wuhan strain) and were higher than those reported at 14 days after the second dose of COVID-19 vaccine (Original, Wuhan strain) of the primary vaccination series. Based on neutralizing antibody responses, non-inferiority was achieved for GMFRs and for the differences in SCRs using the baseline of the first dose of COVID-19 vaccine (Original, Wuhan strain) in the pre crossover period (Cohort 2). Higher immune responses for pseudovirus-based neutralizing antibody against the Omicron BA.4/5 variant and serum IgG antibody against the Omicron BA.1 variant were also seen after the single booster dose of COVID-19 vaccine (Original, Wuhan strain).
Elderly population
COVID-19 vaccine (Original, Wuhan strain) was assessed in individuals 18 years of age and older. The efficacy of COVID-19 vaccine (Original, Wuhan strain) was consistent between elderly (≥ 65 years) and younger individuals (18 to 64 years) for the primary series.
Participants 65 years of age and older were evaluated for efficacy in the two pivotal Phase 3 clinical trials.
In the placebo-controlled Phase 3 study conducted in the United States and Mexico (Study 1 [2019nCoV-301]), 11.8% (n=2,048) of enrolled participants that received the primary series were aged 65 years and older.
In the placebo-controlled Phase 3 study conducted in the United Kingdom (Study 2 [2019nCoV-302]), 27.8% (n=1,953) of enrolled participants that received the primary series were aged 65 years and older.
Immunogenicity data from the Indian studies: ICMR/SII-COVOVAX Study:
Adult cohort (≥ 18 years of age):
This was 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 participants 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/m². 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 (Original, Wuhan strain) is comparable in terms of anti-S IgG antibody titers and seroconversion rates to Novavax vaccine (see Tables 11 and 12).

Table 11: Summary of anti-S IgG antibodies in adults

Timepoint	Statistic	COVOVAX (Original, Wuhan strain) (N=340)	Novavax vaccine (Original, Wuhan strain) (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 12: Summary of proportion of participants with seroconversion for anti-S IgG antibodies in adults

Timepoint	Statistic	COVOVAX (Original, Wuhan strain) (N=340)	Novavax vaccine (Original, Wuhan strain) (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 was 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 (Original, Wuhan strain).
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 were assessed in all participants. Of these 242 were males (52.6%) and 218 were females (47.4%). The median age was 14 years with a range of 12 to 17 years, median BMI was 18.7 kg/m². 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 (Original, Wuhan strain) 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 (Wuhan variant) group. The immunogenicity data indicates that COVOVAX (Original, Wuhan strain) is highly immunogenic in the children of ≥12 to <18 years of age (see Tables 13 and 14).

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

Timepoint	Statistic	COVOVAX (Original, Wuhan strain) (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 14: Summary of proportion of participants with seroconversion for anti-S IgG antibodies in pediatric cohort (≥12 to <18 years of age)

Timepoint	Statistic	COVOVAX (Original, Wuhan strain) (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)	49 (73.1)
	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/m². 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 (Original, Wuhan strain) 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 (Wuhan strain) group. The immunogenicity data indicates that COVOVAX (Original, Wuhan strain) is highly immunogenic in the children of ≥2 to <12 years of age (see Tables 15 and 16).

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

Timepoint	Statistic	COVOVAX (Original, Wuhan strain) (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 16: Summary of proportion of participants with seroconversion for anti-S IgG antibodies in pediatric cohort (≥2 to <12 years of age)

Timepoint	Statistic	COVOVAX (Original, Wuhan strain) (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 was a 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 with either COVISHIELD™ [ChAdOx1 nCov-19 Corona Virus Vaccine (Recombinant)] / COVAXIN® [Whole Virion, Inactivated Coronavirus (SARS-CoV-2) vaccine] at least 6 months ago (6 months / 180 days from the second dose) wherein COVOVAX was administered as a heterologous booster or Covishield / Covaxin were administered as homologous booster in 1:1 ratio in respective cohorts. 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. Covovax as a heterologous booster demonstrated better immune response both against Wuhan as well as omicron.

5.2 PHARMACOKINETIC PROPERTIES
Not applicable.

5.3 PRE-CLINICAL SAFETY DATA
Non-clinical data reveal no special hazard 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 Matrix-M adjuvant. 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 micrograms SARS-CoV-2 rS protein (approximately 200-fold excess relative to the human dose of 5 micrograms on a weight- adjusted basis) with 10 micrograms Matrix-M adjuvant (approximately 40-fold excess relative to the human dose of 50 micrograms on a weight-adjusted basis). No vaccine-related adverse effects on fertility, pregnancy/lactation, or development of the embryo/foetus and offspring through post-natal Day 21 were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Disodium hydrogen phosphate heptahydrate
Sodium dihydrogen phosphate monohydrate
Sodium chloride
Polysorbate 80
Sodium hydroxide (for adjustment of pH)
Hydrochloric acid (for adjustment of pH)
Water for injections

Adjuvant (Matrix-M) Cholesterol
Phosphatidylcholine (including all-rac-α-Tocopherol) Potassium dihydrogen phosphate
Potassium chloride
Disodium hydrogen phosphate dihydrate Sodium chloride
Water for injections

For adjuvant: see also section 2.

6.2 INCOMPATIBILITIES
This medicinal product must not be diluted or mixed with other medicinal products or diluted.

6.3 SHELF-LIFE
Unopened Container
9 months at 2ºC to 8ºC, protected from light.
Unopened COVID-19 Vaccine XBB.1.5 has been shown to be stable up to 12 hours at 25ºC. Storage at 25ºC is not the recommended storage or shipping condition but may guide decisions for use in case of temporary temperature excursions during the 9-month storage at 2ºC to 8ºC.
Single dose vial
Discard the single dose vial after one 0.5 mL dose withdrawal and administration [see Instructions for use/handling]

6.4 SPECIAL PRECAUTION FOR STORAGE
Store in refrigerator (+2 to +8ºC)
Do not freeze
Keep the vials in the outer carton in order to protect from light.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER
- 0.5 mL of dispersion in a vial (type I glass) with a stopper (bromobutyl rubber) and an aluminium overseal with blue plastic flip-off cap.
- Each vial contains 1 dose of 0.5 mL

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
Handling instructions and administration
This vaccine should be handled by a healthcare professional using aseptic techniques to ensure the sterility of each dose.
Preparation for use
- The vaccine comes ready to use.
- Unopened vaccine should be stored at 2ºC to 8ºC and kept within the outer carton to protect from light.
- Immediately prior to use, remove the vaccine container from the carton in the refrigerator.

Inspect the container
- Gently swirl the single-dose vial before the dose withdrawal. Do not shake.
- Each container contains a colourless to slightly yellow, clear to mildly opalescent dispersion practically free from visible particles.
- Visually inspect the contents of the container for visible particulate matter and/or discolorations prior to administration. Do not administer the vaccine if either are present.

Administer the vaccine
- 0.5 mL dose is withdrawn into a sterile needle and sterile syringe to be administered by intramuscular injection, preferably in the deltoid muscle of the upper arm.
- Do not mix the vaccine in the same syringe with any other vaccines or medicinal products.
- Do not pool excess vaccine from multiple vials.

Discard
- Discard single dose vial and excess volume after one dose withdrawal and administration.

Disposal
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER
Manufactured by:
SERUM INSTITUTE OF INDIA PVT. LTD.
S. No. 105-110, Manjari Bk., Pune 412307, India.

8. MARKETING AUTHORIZATION NUMBERS
File No. BIO/MA/23/000137 dated 06th June 2024

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

10. DATE OF REVISION
18.06.2025

200XXXXX/X