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

Whole Virion, Inactivated Coronavirus (SARS-CoV-2) Vaccine

COVAXIN®

1. NAME AND DESCRIPTION OF THE MEDICINAL PRODUCT:
COVAXIN® (Whole Virion Inactivated Coronavirus (SARS-CoV-2) Vaccine) is a white to off white, opalescent suspension, free from extraneous particles containing 6µg of Whole Virion, Inactivated Coronavirus (SARS-CoV-2) Antigen (strain NIV-2020-770) that provides effectiveness with ≥ 110 Geometric Mean Titer (GMT).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each dose of 0.5mL contains:
Whole Virion, Inactivated Coronavirus (SARS-CoV-2) Antigen
(Strain: NIV-2020-770) ..... 6 µg (≥ 110 Geometric Mean Titer (GMT))
Aluminium Hydroxide Gel equivalent to Al*** ..... 0.25 mg
TLR7/8 Agonist ..... 15 µg
2-Phenoxyethanol ..... 2.5 mg
Phosphate Buffered Saline ..... q.s. to 0.5 mL

3. PHARMACEUTICAL FORM
Sterile suspension for injection.

4. CLINICAL PARTICULARS
4.1 Therapeutic indication
COVAXIN® is indicated for active immunization against SARS-CoV-2 virus infection for age ≥ 18 years as per New drug permission.

The vaccine is also permitted to use for the age group of >12 to 18 years for restricted use in an emergency situation in public interest.

4.2 Posology and method of administration.
COVAXIN® should be administered as two doses on Day 0 and Day 28.
Method of administration: Intramuscular injection (IM).
It is recommended that individuals who receive a first dose of **COVAXIN®** should complete the vaccination course with second dose of **COVAXIN®** only.

4.3 Contraindications
- Hypersensitivity to any constituents of the vaccine.

4.4 Special warnings and precautions for use
- Do not administer intravenously, intradermally, or subcutaneously.
- Like all other vaccines, supervision and appropriate medical treatment should always be available to treat any anaphylactic reactions following immunization.
- Concurrent illness: As with other vaccines, administration of **COVAXIN®** should be postponed in individuals suffering from an acute severe febrile illness/acute infection.
- Thrombocytopenia and coagulation disorders: As with other intramuscular injections, **COVAXIN®** should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to persons on anticoagulation therapy, because bleeding or bruising may occur following an intramuscular administration in these individuals.
- Immunocompromised individuals: It is not known whether individuals with impaired immune responsiveness, including individuals receiving immunosuppressant therapy, will elicit the same response as immunocompetent individuals to the vaccine regimen. Immunocompromised individuals may have relatively weaker immune response to the vaccine regimen.
- Interchangeability: No data are available on the use of **COVAXIN®** in persons that have previously received partial vaccine series with another COVID-19 vaccine.
- Vaccinees should remain under medical supervision for at least 15minutes after vaccination.

Before administration, the vaccine vial should be shaken well to obtain a uniform, whitish opalescent suspension. Vial should be visually checked for the presence of any particulate matter or other colouration, if any, prior to its administration. If in doubt, do not use the contents of the vial. **COVAXIN®** should not be mixed with other vaccines.

4.5 Interaction with other medicinal products.
No interaction studies have been performed. Concomitant administrations of **COVAXIN®** with other medicinal products have not been studied.

4.6 Pregnancy and Lactation
Pregnancy
Limited data exists with use of **COVAXIN®** in pregnant women. For additional information please refer section 5.3.4.

Breastfeeding
It is not known whether **COVAXIN®** is excreted in human milk. Data are not available to assess the effects of **COVAXIN®** on the breastfed infant or on milk production/excretion.

4.7 Effects on ability to drive and use machines
No studies on the effect of **COVAXIN®** on the ability to drive and use machines have been performed.However, some of the adverse reactions mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects
Clinical Trial Experience
Safety of the COVAXIN® vaccine was evaluated in the Phase 1, Phase 2 and ongoing Phase 3 studies.

Phase 1 clinical trial[1] (Age: 18–55 Years)
The Phase 1 clinical trial was conducted in India among 375 healthy adult volunteers. The first 50 participants enrolled were monitored for 7 days after vaccination, and on the basis of the independent data safety monitoring board review of masked safety data, the trial was allowed to continue with enrolment of the remaining participants into all groups. Participants were randomly assigned to receive either one of three vaccine formulations (3 µg with Algel-IMDG, 6 µg with Algel-IMDG, or 6 µg with Algel) or an Algel only control vaccine group.After both doses, solicited local and systemic adverse reactions were reported by 17 (17%; 95% CI 10.5–26.1) participants in the 3 µg with Algel-IMDG group, 21 (21%; 13.8–30.5) in the 6 µg with Algel-IMDG group, 14 (14%; 8.1–22.7) in the 6 µg with Algel group, and ten (10%; 6.9–23.6) in the Algel-only group. The most common solicited adverse events were injection site pain (17 [5%] of 375 participants), headache (13 [3%]), fatigue (11 [3%]), fever (9 [2%]), and nausea or vomiting (7 [2%]). All solicited adverse events were mild (43 [69%] of 62) or moderate (19 [31%]) and were more frequent after the first dose. One serious adverse event of viral pneumonitis was reported in the 6 µg with Algel group, unrelated to the vaccine.

Phase 2 clinical trial[2] (Age: 12–65 years)
The Phase 2 clinical trial was conducted in India among 380 adolescents and healthy adult volunteers. Participants were randomly assigned (1:1) to receive either 3 µg with Algel-IMDG or 6 µg with Algel-IMDG. After both doses, the most common solicited adverse events were injection site pain, reported in 5 (2.6% [95% CI 0.9–6.0]) of 190 participants in the 3 µg with AlgelIMDG group and 6 (3.2% [1.2–6.8]) of 190 participants in the 6 µg with Algel-IMDG group. Most adverse events were mild (69 [89%] of 78 participants) and resolved within 24 h of onset. At 7 days after the second dose, solicited local and systemic adverse reactions were reported in 38 (20.0% [14.7–26.5]) of 190 participants in the 3 µg with Algel-IMDG group and 40 (21.1% [15.6–27.7]) of 190 participants in the 6 µg with Algel-IMDG group. No association between the dose of vaccine and the number of adverse events was observed. The most common adverse event in the phase 2 trial was pain at the injection site, followed by headache, fatigue, and fever. No severe or life-threatening (i.e., grade 4 and 5) solicited adverse events were reported. No significant differences in safety were observed between the two groups.

No significant difference in the proportion of participants who had a solicited local or systemic adverse reaction in the 3 µg with Algel-IMDG group (38 [20.0%; 95% CI 14.7–26.5] of 190) and the 6 µg with Algel-IMDG group (40 [21.1%; 15.5–27.5] of 190) was observed on days 0–7 and days 28–35; no serious adverse events were reported in the study.

Phase 3 clinical Trial[3] (Age: > 18 Years)
Safety
BBV152 demonstrated an acceptable safety and reactogenicity profile in adult's ≥18 years of age, including adult's ≥60 years ofage (including those with comorbidities associated with an increased risk of progressing to severe/critical COVID-19). In line with other inactivated vaccines, hypersensitivity reactions following immunization with BBV152 were rare and usually nonserious. Severe allergic (anaphylactic) reactions have not been reported in BBV152 clinical studies to date.

A total of 5959 adverse events (AE's) were reported by 3194 subjects, with a comparable proportion (12.4%) of subjects experiencing at least one AE in the BBV152 and placebo groups. The AEs reported in the BBV152 group were mild (11.2%), moderate (0.8%), or severe (0.3%) and were comparable to the placebo group (mild [10.8%], moderate [1.1%], and severe [0.4%]). A total of 106 serious adverse events (SAE's) were reported by 99 subjects in the study; 40 events in the BBV152 group and 66 events in the placebo group. Overall, the placebo group (60 [0.47%] subjects) had a higher incidence of SAE's as compared to the BBV152 group (39 [0.30%] subjects). Only one SAE (Immune thrombocytopenia) under the System Organ Class of 'blood and lymphatic disorders' was considered related to BBV152 administration. There were 15 deaths in the study, none of which were considered by the investigators to be related to BBV152 or placebo; 6 deaths were reported to be related to COVID-19. In the BBV152 group, there were 5 deaths all due to causes unrelated to vaccination.

These causes included haemorrhagic stroke, metastatic ovarian cancer, cardiac arrest, COVID-19 and sudden cardiac arrest/intracranial haemorrhage (unconfirmed). Ten deaths in the placebo group were due to unrelated conditions and included cardiopulmonary failure, cardiac arrest probably due to acute coronary syndrome and with underlying hypertension, COVID-19 (5 subjects), 1 death with unknown cause and symptoms of headache, and 2 deaths which remain to be determined.

No anaphylactic events were reported.

Approximately 9% of subjects experienced at least one solicited AE within 7 days post vaccination; overall incidence rates of solicited AE's were lower after Dose 2 (4.3% subjects) than Dose 1 (5.9% subjects) and tended to be slightly higher in the BBV152 group than the placebo group. Among the local or systemic solicited AE's, only local injection pain was reported with an incidence >1% after both dose and an overall combined incidence of about 4% across groups. Similar proportions of subjects in BBV152 (3.04%) and placebo (2.78%) groups reported local pain after the first dose, falling to 1.81% and 1.62% subjects after the second dose, respectively. Other frequently reported local AE's included injection site erythema, injection site induration, and injection site swelling, reported by < 0.3% of subjects in any group after either dose.

Solicited systemic AE were reported less frequently in 2.57% and 1.92% subjects after Dose 1; and in 1.8% and 1.6% subjects after Dose 2 in the BBV152 and placebo groups, respectively. The most frequent solicited systemic AE overall was headache, followed by pyrexia, fatigue and myalgia; all with incidences below 1% in both groups. A total of 767 unsolicited AE's was reported from 450 subjects; 1.76% in the BBV152 group and 1.74% in the placebo group. All unsolicited AE's occurred in <1% of subjects with a comparable incidence between BBV152 and placebo groups; the most common events were pyrexia,

cough, headache, and oropharyngeal pain. Immediate AE's within 30 minutes were observed in only 0.1 % of subjects post Dose 1 and 0.04% of subjects post Dose 2. A higher number of immediate AE's within 30 minutes post-dose were observed in the placebo group (29 events, 23 subjects) as compared to the BBV152 group (14 events, 12 subjects); most of these immediate AE's occurred post Dose1. The proportion of subjects experiencing any MAAE's and AESI's were comparable between the BBV152 and placebo groups. Adverse events led to discontinuation of study intervention in overall 19 subjects -13 subjects in the BBV152 group and 6 subjects in the placebo group. Overall, BBV152 exhibited a good reactogenicity profile with similar rates of solicited, unsolicited, and serious adverse events, and AESI's in BBV152 and placebo groups.

Data on medically attended adverse events (MAAE's), serious adverse events (SAE's) and deaths were collected from all 25,798 participants who received a study vaccination and will continue to be collected for a total of 1 year.

Adverse reactions observed during clinical studies are listed below by the frequency categories as:

Very common : (≥1/10)
Common : (≥1/100 to <1/10)
Uncommon : (≥1/1000 to <1/100)
Rare : (≥1/10000 to <1/1000).

Adverse Events observed in Phase 3 clinical trial of BBV152:

MedDRA System Organ Class	Frequency	Adverse reactions
Gastrointestinal disorders	Uncommon	Nausea
	Uncommon	Diarrhoea
General disorders and administration site conditions	Common	Injection site pain, Pyrexia, Fatigue
	Uncommon	Injection site erythema, Injection site induration, Injection site swelling, Injection site pruritus, Chills
Musculoskeletal and connective tissue disorders	Common	Myalgia
	Uncommon	Arthralgia
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
Respiratory, thoracic and mediastinal disorders	Common	Cough
	Uncommon	Oropharyngeal Pain
Skin and subcutaneous tissue disorders	Uncommon	Pruritus

Based on a safety review conducted by the National AEFI (Adverse Event Following Immunization) Committee to the Ministry of Health & Family Welfare, after administration of 6,784,562 doses of BBV152, there were no potential thromboembolic events reported through the CO-WIN platform.

Phase 2/3 clinical Trial in pediatric age group (≤18 to ≥2 years of age):
Safety:

A total of 525 subjects of either gender of ages between ≤18 to ≥2 years were vaccinated in three age groups in age de-escalation manner, 175 in each group. Group 1 (≤18 to ≥12 years of age), Group 2 (≤12 to ≥6 years of age) and Group 3 (≤6 to ≥2 years of age).

Adverse events after 1st dose:

- Among the subjects who were administered the first dose, a total of 244 adverse events were reported. Of the 244 adverse events reported, 232 were solicited adverse events and 12 were unsolicited adverse events.
- Among the 244 adverse events recorded, 22 adverse events were reported immediately within 2 hours of vaccination and 222 adverse events were reported within 7 days of vaccination.
- 160 adverse events were local and 84 adverse events were systemic.
- A total of 240 adverse events were Mild and 4 adverse events were Moderate in severity.

Adverse events after 2nd dose:

- Among the subjects who were administered the second dose, a total of 130 adverse events were reported. Of the 130 adverse events reported, 127 were solicited adverse events and 3 were unsolicited adverse events.
- Among the 130 adverse events recorded, 10 adverse events were reported immediately within 2 hours of vaccination and 120 adverse events were reported within 7 days of vaccination.
- 100 adverse events were local and 30 adverse events were systemic
- A total of 128 adverse events were Mild and 2 adverse events were Moderate in severity.
- No serious adverse event was reported in the study.

All the 374 adverse events were either mild or moderate in severity, and pain at the injection site was the most commonly reported adverse event. The other common adverse events that were reported are fever, headache, body pains, redness at injection site, swelling at injection site, fatigue, vomiting, cough, itching, redness of eye, shoulder pain.

Most of the adverse effects were mild in nature and resolved. Majority of the adverse events, about 78.6% resolved within 24 hours. These 374 adverse events were reported in 222 volunteers, which is about 42.2% of the total volunteers.

Adverse reactions observed during clinical studies are listed below by the frequency categories as:

Very common : (≥1/10)
Common : (≥1/100 to <1/10)
Uncommon : (≥1/1000 to <1/100)
Rare : (≥1/10000 to <1/1000).

Adverse Events observed with BBV152 in Phase 2/3 clinical trial in pediatric age group (≤18 to ≥2 years of age):

MedDRA System Organ Class	Frequency	Adverse reactions		
		≤18 to ≥12 years of age	≤12 to ≥6 years of age	≤6 to ≥2 years of age
Eye disorders	Uncommon	Ocular hyperaemia	Eye pain	Ocular hyperaemia
Gastrointestinal disorders	Common	-	Vomiting	-
	Uncommon	Vomiting, Diarrhoea	Nausea, Abdominal discomfort, Abdominal pain	-
General disorders and administration site conditions	Very Common	Injection site pain, Pyrexia	Injection site pain, Pyrexia	Injection site pain, Pyrexia
	Common	-	Injection site erythema, Injection site swelling	Injection site erythema
	Uncommon	-	Tenderness, Asthenia, decreased appetite, Fatigue	Injection site swelling, Fatigue
Musculoskeletal and connective tissue disorders	Common	Arthralgia	-	-
	Uncommon	Pain in extremity	Musculoskeletal stiffness, Pain in extremity	-
Nervous system disorders	Very common	-	Headache	-
	Common	Headache	-	-
Respiratory, thoracic and mediastinal disorders	Uncommon		Oropharyngeal pain, Sneezing	Cough, Nasopharyngitis
Skin and subcutaneous tissue disorders	Common	-	Pruritus	-

4.9 Overdose:

There is no specific treatment for an overdose with **COVAXIN®**. In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

COVID-19 disease is caused due to SARS-CoV-2 virus infection. **COVAXIN®** has been studied in Phase 1 and 2 clinical studies for safety and immunogenicity and found to be safe and immunogenic. In the ongoing Phase 3 trial, **COVAXIN®** has been shown to prevent COVID-19 following 2 doses of vaccine given 4 weeks apart based on the interim analysis showing vaccine efficacy to be 77.8%. The duration of protection against COVID-19 is currently unknown.

Immune Response and Efficacy

COVID-19 disease is caused due to SARS-CoV-2 virus infection.

Immunogenicity studies in humans;
Phase 1 clinical trial[1]

The Phase 1 trial showed seroconversion rates (%) were 91.9% in the 6 µg with Algel-IMDG post dose 2. Post 28 days second-dose Geometric mean titres (GMTs) were 66.4 [95% CI 53.4–82.4] in the 6 µg Algel-IMDG group based on MNT_{90}. CD4+ and CD8+ T-cell responses were detected in a subset of 8 participants from 6 µg Algel-IMDG groups. Additionally, IgG using ELISA assays were determined against spike (S1) glycoprotein, receptor-binding domain, and nucleocapsid protein of SARS-CoV-2 increased rapidly after the administration of the two-dose regimen. The mean isotyping ratios (IgG1/IgG4) were greater than 1 for the vaccinated group, which was indicative of a Th1 bias in immune response.

Three months after dose two receipts, follow up serum samples were collected from the Phase 1 study participants. In the 6 µg group, GMTs (MNT_{90}) at day 104 were 69.5 [95% CI 53.7–90.0]. Seroconversion based on MNT_{90} was reported in 76 (81.1% [95% CI 71.4–88.1]) participants in the 6 µg with Algel-IMDG group. This suggests that GMTs were maintained after 28 days post dose two and 104 days. T-cell memory responses were also evaluated and found to be persistent among phase 1 vaccine recipients.

Phase 2 clinical trial[2]

In the phase 2 trial, for the 6 µg Algel-IMDG group similar results were found with GMTs plaque reduction neutralization test ($PRNT_{50}$) at day 0 of 0.10 [95% CI 0.09-0.11], which then increased to 197 0 (95% CI 155.6–249.4) at day 56. Seroconversion based on $PRNT_{50}$ at day 56 was reported in 174 (98.3% [95% CI 95.1-99.7]) of 177 participants.

GMTs (MNT_{50}) at day 56 were160.1 (95% CI 135.8–188.8). Seroconversion based on MNT_{50} at day 56 was reported in 171 (96.6% [95% CI 92.6–98.5]) of 177 participants. IgG antibody titres (GMTs) to all epitopes (spike glycoprotein, receptor-binding domain, and nucleocapsid protein) were detected after the administration of the vaccine. The Th1/Th2 cytokine ratio indicated bias to a Th1 cell response at day 42.

Immunogenicity studies against Variants of Concern[4-7]:
Neutralizing antibody titres ($PRNT_{50}$) of sera collected (4 weeks after the second dose) from 38 vaccine recipients, who received the BBV152 vaccine candidate in the Phase 2 trial (no evidence of previous SARS CoV-2 infection) were evaluated to determine the immunogenicity of the BBV152 vaccine candidate against of the three different virus strains including VOC Alpha (B.1.1.7). A representative set of 20 serum samples of vaccine recipients were also tested to serve as comparison samples. Using $PRNT_{50}$ values from these groups showed a non-significant difference (P > 0.05) in neutralization between the three tested strains.

Further immunogenicity studies were done as described as follows: using sera of 28 BBV152 vaccinated individuals (no evidence of previous SARS CoV-2 infection), collected during the Phase 2 clinical trial and sera samples collected from COVID-19 recovered individuals (n=17) $PRNT_{50}$ testing was conducted. This demonstrated that neutralizing capacity against Delta Variants of Concern (VOC) (B.1.617.1) was similar from sera of vaccinated individuals and that of recovered cases. Another study was done to determine the IgG immune response and neutralizing activity of 19 convalescent sera specimens obtained from recovered cases of COVID-19 and confirmed for VOC Alpha (B.1.1.7, [n = 2]), Beta (B.1.351 [n =2]), B.1.1.28.2 (n = 2), B1 lineage (n = 13) (15–113 days post positive test). The data were compared with sera from 42 participants immunized with BBV152 as part of Phase 2 clinical trial (2 months post the second dose). This study found a high level of cross-neutralization in sera collected from variant infected individuals compared to those vaccinated with BBV152. One other study was reported where the neutralization antibodies in sera collected from COVID-19 recovered cases (n=20) and vaccinees with two doses of BBV152 (n=17) against VOC Beta (B.1.351) and VOC Delta (B.1.617.2) compared. While there was a reduction in neutralization titers insera of COVID-19 recovered cases (3.3-fold and 4.6-fold) and BBV152 vaccinees (3. 0 and 2.7-fold) against VOC Beta (B.1.351) and VOC Delta (B.1.617.2) respectively, there was cross neutralization against these two VOCs.

Phase 3 clinical trial[3]
Efficacy
The phase 3 study is an ongoing, multi-center, randomized, double-blind, placebo-controlled in India that assesses the efficacy, safety, and immunogenicity of a two-dose regimen of BBV152 for the prevention of symptomatic COVID-19 in adults aged 18 years and older. The study is being conducted in 25 different sites in India. A total of 25,798 participants were randomized of whom 24,419 were vaccinated with either two doses of BBV152 or placebo. The study included adults over 18 years of age who were healthy or had stable medical conditions. It was relatively well-balanced among subgroups with regard to age, comorbidities and sex. The study enrolled participants at 25 sites with the ability to conduct RT PCR and serology for COVID-19, from November 16, 2020 to January 7, 2021. The time of study enrolment coincided with the emergence of new SARS-CoV-2 variants; some participants within the study included these variants of concern. Efficacy results were based on the primary analysis, which included 12,879 participants who received the vaccine and 12,874 participants who received placebo, as first dose. This interim analysis included data up to May 17, 2021 and included a median of 146 days of safety data available after the first dose and a median of 99 days of efficacy follow up two weeks after a second dose.

At the time of the reported per-protocol analysis, 130 laboratory-confirmed primary endpoint cases were observed with an onset at least 14 days after vaccination with dose 2. Of these cases, 24 occurred in the vaccinated group and 106 (occurred in the placebo group. The vaccine efficacy was found to be 77.8% (95% CI: 65.2 - 86.4). Further analysis was conducted to look at secondary endpoints including severe disease. In this analysis a total of 16 participants (1 vaccine recipient, 15 placebo recipients) yielding a vaccine efficacy of 93.4% (95% CI: 57.1–99.8) against severe disease.

In the analysis of confirmed symptomatic COVID-19 cases a total of 79 variants were reported from 16,973 samples, 18 in the vaccine and 61 in the placebo group. Among 50 Delta (B.1.617.2) positive-confirmed cases, 13 and 37 participants were in the vaccine and placebo arms, resulting in vaccine efficacy of 65.2% (95% CI: 33.1–83.0).

The study design also included routine monthly PCR testing, therefore, the investigators were able to determine efficacy against asymptomatic COVID-19 was 63.6% (95% CI: 29.0-82.4), with a total of 46 asymptomatic cases (13 in vaccine recipients and 33 in placebo recipients) (n = 6289).

Immunogenicity:
The GMT values for SARS-CoV-2 specific nAb were comparable across all groups at Day 0. At Day 56, in the groups who received BBV152 Lots 1, 2, 3, or placebo, the GMTs of SARS-CoV-2 nAb were 130.3 [95% CI: 105.8 - 160.4], 121.2 [95% CI: 97.6 - 150.5], 125.4 [95% CI: 101.3 – 155.1], and 13.7 [95% CI: 10.7 - 17.4], respectively. The point estimate of GMT [95% CIs] ratios for SARS-CoV-2 specific neutralizing antibody between all three pairs of lots were consistently similar: 1.075 [0.798 - 1.449] in Lot 1 vs. Lot 2; 1.039 [0.772 - 1.398] in Lot 1 vs. Lot 3; and 0.966 [0.714 - 1.308] in Lot 2 vs. Lot 3. All the 95% CIs for the GMT ratios were contained within [0.5 - 2.0] for INDIA and [0.67 - 1.5] for US-FDA, thus, meeting the predefined criterion for consistent immune response across lots.

Immunogenicity (Phase 2/3 clinical Trial in pediatric age group (Age: >2 to <18 years):
On Day 56, in MNT_{50} a total of 90.29% in group 1, 89.81% in group 2 and 100% in group 3 achieved ≥4 Fold rise in titres and in $PRNT_{50}$ a total of 94.3% in group 1, 98.81% in group 2 and 98.26% in group 3 achieved ≥4 Fold rise in titres (seroconverted).

On Day 56, using ELISA, in S1, a total of 97.14% in group 1, 95.29% in group 2 and 90% in group 3 achieved ≥4 Fold rise in titres (seroconverted). In RBD, 87.43% in group 1, 92.35% in group 2 and 91.43% in group 3 were seroconverted. In NP, 95.43% in group 1, 92.94% in group 2 and 87.14% in group 3 were seroconverted.

5.2 Pharmacokinetic properties:
Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data
Adjuvant (Algel-IMDG) safety: In the **COVAXIN®** development, an adjuvant named Algel-IMDG was used which is a novel adjuvant used for the first time in human clinical trials against SARS CoV-2. Algel-IMDG constitutes TLR7/8 agonist (m-Amine Gallamide) a novel Imidazoquinoline class molecule chemisorbed on to aluminium hydroxide. This Adjuvant formulation technology was licensed from VIROVAX, Lawrence, KS, USA. Algel-IMDG was tested in several animal models against several vaccine candidates both by VIROVAX and BBIL. Briefly, Algel-IMDG is an Algel on which IMDG was chemisorbed to traffic vaccine antigen directly to draining lymph nodes without diffusing into the systemic circulation. It has undetectably low systemic exposure and attendant reactogenicity. Given its first in human clinical trials use against SARS CoV-2 in **COVAXIN®**, extensive safety evaluation was performed wherein, Algel-IMDG neither showed any treatment related changes either by clinical pathological or histopathological investigations, nor showed any erythema, edema, or any other macroscopic lesions at the site of injection. Thus, it was considered that Algel-IMDG is safe at the given concentration and shown to induce Th1 biased immune response demonstrated in the pre-clinical studies as detailed below. Broadly, Algel-IMDG when used as an adjuvant, helps in enhancing the immune response, by activating the innate immune system in-turn inducing adaptive immune response, which could provide broader & long-lasting immune response against specific antigen.

5.3.1 Safety and immunogenicity in Mice, Rats, and Rabbits[8]:
Three animal models were used to evaluate the immunogenicity and safety of the three inactivated whole virion vaccine formulations (BBV152 A, B & C).

Study was conducted with an equal number of males and females unless otherwise specified. The control group was injected with saline. Animals were bled from the retro-orbital plexus; 2hours before each immunization on 0, 7, 14 & 21 days, and serum was separated and stored at -20°C until further use.

Pooled and individual sera from vaccinated mice and rabbits were used to test the antigen-specific antibody binding titer and antibody isotyping profile by Enzyme-Linked Immunosorbent Assay (ELISA). Pooled or Individual sera from all vaccinated species (mice, rabbits & rats) were used to test neutralization antibody titer by Plaque Reduction Neutralization Test ($PRNT_{50}$) or Micro Neutralization Test (MNT_{50}).

Both the adjuvanted vaccines (with Algel and Algel-IMDG), Antigen and Adjuvant alone did not reveal any treatment-related findings, except local reactions when administered through the human intended route (intramuscular) on days 0, 7, and 14 (n+1) with full Human single dose (HSD) or higher than HSD in rodents and non-rodents, thereby establishing the vaccine safety.

BBV152 vaccine formulations generated significantly high antigen-binding and neutralizing antibody titers, at both concentrations, in all three species with excellent safety profiles. The inactivated vaccine formulation containing TLR7/8 agonist adjuvant-induced Th1 biased antibody responses with elevated IgG2a/IgG1 ratio and increased levels of SARS-CoV-2 specific IFN-γ + CD4 T lymphocyte response.

5.3.2 Immunogenicity and protective efficacy in the Syrian hamsters[9]
Two formulations of BBV152 vaccine (3 µg and 6 µg) and 2 adjuvants namely Algel 1 (Alum) and Algel 2 (TLR 7/8 (Imidazoquinoline) agonist adsorbed alum) in combinations were used for the study. The vaccine formulations evaluated in the study were 6 µg antigen with Algel1, 3 µg with Algel 2, and 6 µg with Algel 2. Accordingly, the animals were divided into 4 groups (9 animals/per groups).

Animals of each group were immunized with 0.1 ml of PBS/vaccine formulations intramuscularly in the left hind leg under isoflurane anaesthesia 0, 14, and 35 days. Post immunization hamsters were observed daily for clinical signs and injection site reaction. Rectal temperature was monitored every 24 hours for 3 days post-immunization and weekly thereafter. Body weight was measured every alternate day for the first week and weekly thereafter. The hamsters were bled on day 12, 21, and 48 post-immunization to check for antibody response.

Challenge study in hamsters
The immunized hamsters were challenged with 0.1 ml of $10^{5.5}$ TCID50 SARS-CoV-2 virus intranasally on the eighth-week post-immunization (day 50) in the containment facility of ICMR-National Institute of Virology, Pune under isoflurane anaesthesia.

Three dose vaccination regimes with three formulations of BBV152 induced significant titres of SARS-CoV-2 specific IgG and neutralizing antibodies (Figure 5). The formulation with Imidazoquinoline Gallamide adsorbed on alum adjuvant remarkably generated a quick and robust immune response.These findings confirm the immunogenic potential of BBV152 and further protection of hamsters challenged with SARS-CoV-2.

5.3.3 Immunogenicity and protective efficacy in rhesus macaques[10]
Twenty macaques were divided into four groups of five animals each. One group was administered a placebo while three groups were immunized with three different vaccine candidates at 0 and 14 days.

The protective response was observed with increasing SARS-CoV-2 specific IgG and neutralizing antibody titers from 3rd-week post-immunization. Weight loss, pyrexia and worsening of SpO2 at room air, lethargy, reduced food and water intake, reduced self-grooming was observed in placebo group and persisted till 7 DPI whereas these features resolved in the other group II and IV. Viral clearance was observed from bronchoalveolar lavage fluid, nasal swab, throat swab, and lung tissues at 7 days post-infection in the vaccinated groups. No evidence of pneumonia was observed by histopathological examination in vaccinated groups, unlike the placebo group which showed features of interstitial pneumonia and localization of viral antigen in the alveolar epithelium and macrophages by immunohistochemistry.

The study demonstrates that a two-dose vaccination regimen induced a significant immune response and provided effective protection in animals challenged with SARS-CoV-2 virus.

5.3.4 Developmental And Reproductive Toxicity Study:
DART study was conducted in New Zealand White Rabbits with **COVAXIN®** and Algel – IMDG with human intended dose intramuscularly as per the regulatory guidelines (WHO guidelines 2013, ICH S5 (R3) guideline 2020, CIH New Drugs and Clinical Trial Rules, 2019). No treatment related abnormalities such as clinical signs, feed consumption, body weight gain, placental weights, were found in both pre-natal and post-natal groups of **COVAXIN®** and Algel-IMDG, compared to Phosphate Buffer Saline group. Similarly, no abnormalities found in uteri of Does, including the number of implantation sites and no external malformations were observed in foetuses or pups. Gross pathology and histopathology examination found normal in Does, pups / fetus from both pre-natal or post-natal groups. Maternal transfer of antibodies (IgG) from Does to fetuses (50%) in the pre-natal subgroup, suggestive of passive immunity, during the early life.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Aluminium hydroxide gel, TLR7/8 Agonist, 2-Phenoxyethanol, Phosphate Buffered Saline

6.2 Incompatibilities
The vaccine should not be mixed with any other medicinal products or active immunizing agents.

6.3 Shelf life
The expiry date of **COVAXIN®** is indicated on the label and carton of the vaccine. Do not use the vaccine after the expiration date shown on the label and carton of the vaccine.

6.4 Special precautions for storage
Store at +2° to +8 °C, do not freeze. Discard if frozen. Shake well before use.
Keep out of reach of children. Protect from light.
Store vials in the original carton till the vial is used.

7. PRESENTATION

COVAXIN® is presented in USP type 1-glass vials.

Single dose vial	: 0.5mL
Multi dose vial	: 2.5mL (5 dose)
Multi dose vial	: 5.0mL (10 dose)
Multi dose vial	: 10.0mL (20 dose)

Opened vials may be used in subsequent immunization session for up to a maximum of 28 days provided that all of the following conditions are met (as described in the WHO policy statement: Multi-dose vial Policy (MDVP) Revision 2014 WHO/IVB/14.07).

- The expiry date of the vaccine has not passed.
- The vaccine is approved for use for up to 28 days after opening the vial, as determined by WHO
- Vaccinator should record the date and month, when the vial is opened.
- The vaccine vial has been, and will continue to be, stored at +2°C to +8°C
- The vaccines are stored under appropriate cold chain conditions.
- The vaccine vial septum has not been submerged in water.
- The aseptic technique has been used to withdraw all doses.
- An opened vial must be discarded immediately if any of the following conditions apply.
  - Sterile procedures have not been fully followed.
  - There is even a suspicion that the opened vial has been contaminated.
  - There is visible evidence of contamination.
  - If the vaccine vial is frozen or breakage in the continuity of the vials (crack/leaks).

8. REFERENCES

1. Ella R, Vadrevu KM, Jogdand H, Prasad S, Reddy S, Sarangi V, Ganneru B, Sapkal G, Yadav P, Abraham P, Panda S, Gupta N, Reddy P, Verma S, Kumar Rai S, Singh C, Redkar SV, Gillurkar CS, Kushwaha JS, Mohapatra S, Rao V, Guleria R, Ella K, Bhargava B. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. Lancet Infect Dis. 2021 May;21(5):637-646. doi: 10.1016/S1473-3099(20)30942-7. Epub 2021 Jan 21. Erratum in: Lancet Infect Dis. 2021 Apr;21(4):e81. PMID: 33485468; PMCID: PMC7825810.

2. Ella R, Reddy S, Jogdand H, Sarangi V, Ganneru B, Prasad S, Das D, Raju D, Praturi U, Sapkal G, Yadav P, Reddy P, Verma S, Singh C, Redkar SV, Gillurkar CS, Kushwaha JS, Mohapatra S, Bhate A, Rai S, Panda S, Abraham P, Gupta N, Ella K, Bhargava B, Vadrevu KM. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. Lancet Infect Dis. 2021 Jul;21(7):950-961. doi: 10.1016/S1473-3099(21)00070-0. Epub 2021 Mar 8. PMID: 33705727; PMCID: PMC8221739.

3. Ella R, Reddy S, Blackwelder W, Potdar V, Yadav P, Sarangi V, Aileni VK, Kanungo S, Rai S, Reddy P, Verma S, Singh C, Redkar S, Mohapatra S, Pandey A, Ranganadin P, Gumashta R, Multani M, Mohammad S, Bhatt P, Kumari L, Sapkal G, Gupta N, Abraham P, Panda S, Prasad S, Bhargava B, Ella K, Vadrevu KM; COVAXIN Study Group. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double blind, controlled, phase 3 trial. Lancet. 2021 Nov 11:S0140-6736(21)02000-6. doi: 10.1016/S0140-6736(21)02000-6. Epub ahead of print. PMID: 34774196; PMCID: PMC8584828.

4. Sapkal GN, Yadav PD, Ella R, Deshpande GR, Sahay RR, Gupta N, Vadrevu KM, Abraham P, Panda S, Bhargava B. Inactivated COVID-19 vaccine BBV152/COVAXIN effectively neutralizes recently emerged B.1.1.7 variant of SARS-CoV-2. J Travel Med. 2021 Jun 1;28(4):taab051. doi: 10.1093/jtm/taab051. PMID: 33772577; PMCID: PMC8083765.

5. Yadav PD, Sapkal GN, Abraham P, Ella R, Deshpande G, Patil DY, Nyayanit DA, Gupta N, Sahay RR, Shete AM, Panda S, Bhargava B, Mohan VK. Neutralization of variant under investigation B.1.617 with sera of BBV152 vaccinees. Clin Infect Dis. 2021 May 7:ciab411. doi: 10.1093/cid/ciab411. Epub ahead of print. PMID: 33961693.

6. Sapkal G, Yadav PD, Ella R, Abraham P, Patil DY, Gupta N, Panda S, Mohan VK, Bhargava B. Neutralization of VUI B.1.1.28 P2 variant with sera of COVID-19 recovered cases and recipients of Covaxin an inactivated COVID-19 vaccine. J Travel Med. 2021 Oct 11;28(7):taab077. doi: 10.1093/jtm/taab077. PMID: 34002240; PMCID: PMC8194512.

7. Yadav PD, Sapkal GN, Ella R, Sahay RR, Nyayanit DA, Patil DY, Deshpande G, Shete AM, Gupta N, Mohan VK, Abraham P, Panda S, Bhargava B. Neutralization of Beta and Delta variant with sera of COVID-19 recovered cases and vaccinees of inactivated COVID-19 vaccine BBV152/Covaxin. J Travel Med. 2021 Oct 11;28(7): taab104. doi: 10.1093/jtm/taab104. PMID: 34230972; PMCID: PMC8344909.

8. Ganneru B, Jogdand H, Daram VK, Das D, Molugu NR, Prasad SD, Kannappa SV, Ella KM, Ravikrishnan R, Awasthi A, Jose J, Rao P, Kumar D, Ella R, Abraham P, Yadav PD, Sapkal GN, Shete-Aich A, Desphande G, Mohandas S, Basu A, Gupta N, Vadrevu KM. Th1 skewed immune response of whole virion inactivated SARS CoV 2 vaccine and its safety evaluation. iScience. 2021 Apr 23;24(4):102298. doi: 10.1016/j.isci.2021.102298. Epub 2021 Mar 10. PMID: 33723528; PMCID: PMC7944858.

9. Mohandas S, Yadav PD, Shete-Aich A, Abraham P, Vadrevu KM, Sapkal G, Mote C, Nyayanit D, Gupta N, Srinivas VK, Kadam M, Kumar A, Majumdar T, Jain R, Deshpande G, Patil S, Sarkale P, Patil D, Ella R, Prasad SD, Sharma S, Ella KM, Panda S, Bhargava B. Immunogenicity and protective efficacy of BBV152, whole virion inactivated SARS- CoV-2 vaccine candidates in the Syrian hamster model. iScience. 2021 Feb 19;24(2):102054. doi: 10.1016/j.isci.2021.102054. Epub 2021 Jan 9. PMID: 33521604; PMCID: PMC7829205.

10. Yadav PD, Ella R, Kumar S, Patil DR, Mohandas S, Shete AM, Vadrevu KM, Bhati G, Sapkal G, Kaushal H, Patil S, Jain R, Deshpande G, Gupta N, Agarwal K, Gokhale M, Mathapati B, Metkari S, Mote C, Nyayanit D, Patil DY, Sai Prasad BS, Suryawanshi A, Kadam M, Kumar A, Daigude S, Gopale S, Majumdar T, Mali D, Sarkale P, Baradkar S, Gawande P, Joshi Y, Fulari S, Dighe H, Sharma S, Gunjikar R, Kumar A, Kalele K, Srinivas VK, Gangakhedkar RR, Ella KM, Abraham P, Panda S, Bhargava B. Immunogenicity and protective efficacy of inactivated SARS-CoV-2 vaccine candidate, BBV152 in rhesus macaques. Nat Commun. 2021 Mar 2;12(1):1386. doi: 10.1038/s41467-021-21639-w. PMID: 33654090; PMCID: PMC7925524.

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