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INDIA'S WEAPON TO FIGHT AGAINST CORONAVIRUS- COVAXIN (COVID19 VACCINE)

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ABSTRACT

Since the pandemic began (COVID19), India has confirmed more than 38 million cases and over 487,719 deaths. The country has recorded the second-highest number of Covid-19 infections in the world after the United States. India launched first home-made vaccine "Covaxin" in January, 2021 to eradicate the corona virus.Bharat Biotech International Limited in collaboration with Indian Council of Medical Research (ICMR) has developed an inactivated whole virion COVID-19 vaccine, COVAXIN. The COVAXIN has been evaluated for its safety, reactogenicity and immunogenicity in phase 1 and 2 clinical trials and the trial reports were submitted to the Central Drugs Standard Control Organization (CDSCO) India. The double-dose vaccine showed significantly higher neutralizing antibody responses in Phase II than in Phase I due to the difference in dosing regimens that changed to a 4-week apart injection schedule from a 2-week course. by December 31, 89.4% of adults had received their first dose and 64.2% had been fully vaccinated The purpose of the paper is to aware the whole community regarding the India's first developed vaccine COVAXIN, its safety and efficacy, adverse effects and minimum complications like others vaccine. This is one of the promising weapons to fight against unknown COVID19, the silent killer. As per Government circular the price of Covid vaccines (COVAXIN) at private hospitals at Rs 1410 per dose. The reasonable cost of the vaccine, the common people can easily take the vaccine to protect from corona virus. So, India's developed vaccine COVAXINtakes a role to eradicate the coronavirus in the near future and save millions of people's lives against COVID19.

Keywords: Covid-19, Covaxin, India Vaccine, Virus, Bharat Biotech, Virology

INTRODUCTION-

COVAXIN is included along with immune-potentiators, also known as vaccine adjuvants, which are added to the vaccine to increase and boost its immunogenicity. It is a 2-dose vaccination regimen given 28 days apart. The COVID-19 pandemic has been a disaster of unprecedented proportions worldwide and specifically in India. India has had some of the highest figures of infection due to the virus with extended high mortality. It hit the country around mid-March 2020. Since then, the crisis has led to several challenges disrupting life in all aspects, especially the socio-economical and medical impacts. As of January 19, the official number of infected cases was more than 38 million, And (more than 4 lakh approx..) dead reported ministry of health and family welfare, Government of India.

COVAXIN, which is an indigenous COVID-19 vaccine to fight against corona virus, has been developed by Bharat Biotech in collaboration with Indian Council of Medical Research (ICMR) and National Institute of Virology (NIV). Whole-Virion Inactivated Vero Cell derived platform technology was used to developed the vaccine. The Vero cell manufacturing platform has an excellent safety record of more than 300 million doses. The inactivated vaccines cannot possibly replicate and are thus cannot likely revert and cause pathological effects. They are manufactured using deadvirus, incapable of infecting people but still able to instruct the immune system to mount a defensive reaction against an infection.

About COVAXIN

Covaxin is a vaccine granted approval for restricted use in emergency situation that may prevent COVID-19. The Central Licensing Authority (CDSCO) has granted permission for the sale or distribution of COVAXIN for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode . In phase 1 and phase 2 clinical trials, Covaxin has demonstrated the ability to produce antibodies against COVID-19.

Key Features of COVAXIN:

I. COVAXIN included along with immune-potentiators, also known as vaccine adjuvants, which are added to the vaccine to increase and boost its immunogenicity.
II. It is a 2-dose vaccination regimen given 28 days apart.
III. It is a vaccine with no sub-zero storage, no reconstitution requirement,and ready to use liquid presentation in multi-dose vials, stable at 2-8 C°
IV. Pre-clinical studies: Demonstrated strong immunogenicity and protective efficacy in animal challenge studies conducted in

hamsters & non-human primates. For more information about our animal study, please visit our blog page on Non-Human Primates.

V. The vaccine received DCGI approval for Phase I & II Human Clinical Trials in July, 2020.

VI. A total of 375 subjects have been enrolled in the Phase 1 study and generated excellent safety data without any reactogenicity. Vaccine-induced neutralizing antibody titers were observed with two divergent SARS-CoV-2 strains. Percentage of all the side-effects combined was only 15% in vaccine recipients. In Phase 2 study, 380 participants of 12-65 years were enrolled. COVAXIN led to tolerable safety outcomes and enhanced humoral and cell-mediated immune responses.

Mechanism of action of COVAXIN-

COVAXIN is an inactivated vaccine obtained from the SARS-CoV-2 strain. The vaccine is used along with immune stimulants, commonly known as vaccine adjuvants (Alhydroxiquim- II), to improve immune response and longer-lasting immunity. The vaccine candidate is produced through the formulation of the inactivated virus with Kansas-based ViroVax's Alhydroxiquim-II adjuvant .COVAXIN mainly contains 6µg of whole-virion inactivated SARS-CoV-2 antigen (Strain: NIV-2020-770), and the other inactive components such as 250µg aluminium hydroxide gel, 15µg TLR 7/8 agonist (imidazoquinolinone), 2.5mg TM 2- phenoxyethanol, and phosphate buffer saline up to 0.5ml. The vaccine requires no sub-zero storage and reconstitution requirement and available [5]

PRODUCT SUMMARY-

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 6 µg of Whole Virion, Inactivated (SARS-CoV-2) Antigen (strain NIV-2020-770).
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**
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. CLINICAL PARTICULARS:

Sterile suspension for injection.

Therapeutic indication

COVAXIN® is indicated for active immunization against SARS-CoV-2 Virus infection for age ≥18years. The vaccine is permitted for restricted use in emergency situation in public interest, under the provisions of New Drugs and Clinical Trials Rules, 2019, the Drugs & Cosmetics Act 1940.

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** complete the vaccination course with **COVAXIN**

Contraindications

- Hypersensitivity to any constituents of the vaccine.

Interaction with other medicinal products.

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

Pregnancy and Lactation

Safety, efficacy, and immunogenicity have not been established in pregnant women and nursing mothers, though vaccine is permitted in lactating mothers. Available data on COVAXIN® Vaccine administered to pregnant women are insufficient to inform vaccine associated risks in pregnancy.

The use of COVAXIN® in pregnant women is recommended only if the benefits of vaccination to the pregnant woman outweigh the potential risks. To help pregnant women make this assessment, they should be provided with information about the risks of COVID-19 in pregnancy (including, for example, that some pregnant women are at increased risk of infection or have co-morbidities

that add to their risk of severe disease), the likely benefits of vaccination in the local epidemiologic context, and the current limitations of the safety data in pregnant women.[8]

Clinical trials Phase I and II Trials

In May 2020, Indian Council of Medical Research's (ICMR's) National Institute of Virology approved and provided the virus strains for developing a fully indigenous COVID- 19 vaccine. In June 2020, the company received permission to conduct Phase I and Phase II human trials of a developmental COVID-19 vaccine codenamed **BBV152**, from the Drugs Controller General of India (DCGI), Government of India. A total of 12 sites were selected by the Indian Council for Medical Research for Phase I and II

randomised, double-blind and placebo-controlled clinical trials of vaccine candidate. [1,2]

In January 2021, the company published Phase I trial results in *The Lancet*. On 8 March 2021, Phase II results were published in *The Lancet*. The study showed that Phase II trials had a higher immune response and induced T-cell response due to the difference in dosing regime from Phase I. The doses in Phase II were given at 4 weeks interval as opposed to 2 weeks in Phase I. Neutralization response of the vaccine were found significantly higher in Phase II. [1,2]

Phase III trials

In November 2020, Covaxin received the approval to conduct Phase III human trials after completion of Phase I and II. A randomised, double-blinded, placebo-controlled study among volunteers of age group 18 and above, it started on 25 November and involved around 26,000 volunteers from across 22 sites in India. Refusal rate for Phase III trials was much higher than that for Phase I and Phase II. As a result, only 13,000 volunteers had been recruited by 22 December with the number increasing to 23,000 by 5 January.

Multiple ethical breaches have been reported at one of their trial sites in Bhopal, potentially hampering the quality of overall data. [3]

Phase IV trials

In June 2021, Bharat Biotech announced the start of phase IV trials to evaluate the vaccine's real-world effectiveness. A study of effectiveness and hesitancy study in Healthcare Workers of Max Group of Hospitals at New Delhi from Covaxin and Covishied is under trials. [4]

Trials on minors

In May 2021, Drugs Controller General of India (DCGI) approved clinical trials in the age group of 2 to 18 years. The trials are conducted at AIIMS Delhi and Patna. As many as 54 children had registered at the AIIMS Patna. In total 525 participants are enrolled in the study as per clinical trial data.

Immune Response and Efficacy

COVID-19 disease is caused due to SARS-CoV-2 virus infection. Immunogenicity studies in humans (Phase 1 and 2)

The Phase 1 trial showed seroconversion rates (%) were 91·9% in the 6 mcg 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 mcg Algel IMDG group based on MNT50. CD4+ and CD8+ T-cell responses were detected in a subset of 8 participants from 6 mcg 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 receipt, follow up serum samples were collected from the Phase 1 study participants. In the 6mcg group, GMTs (MNT50) at day 104 were 69·5 [95% CI 53·7 – 90.0]. Seroconversion based on MNT50 was reported in 76 (81·1% [95% CI 71·4 –88·1]) participants in the 6 mcg 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.

In the phase 2 trial, for the 6mcg Algel-IMDG group similar results were found with GMTs plaque reduction neutralization test (PRNT50) 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 PRNT50 at day 56 was reported in 174 (98·3% [95% CI 95·1 –99·7]) of 177 participants. GMTs (MNT50) at day 56 were160·1 (95% CI 135·8–188·8). Seroconversion based on MNT50 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.[6]

Immunogenicity studies against Variants of Concern:

Neutralizing antibody titres (PRNT50) of sera collected (4 weeks after the second dose) from 38 vaccine recipients, who received the BBV152 vaccine candidate in the Phase II 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 PRNT50 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 II clinical trial and sera samples collected from COVID-19 recovered individuals (n=17) PRNT50 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 II clinical trial (2 months post the second dose). This study found a high levels 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 in sera 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 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).[7]

- **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 neutralising 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 1vs. 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.[8]

Overdose:

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

COVID-19 disease is caused due to SARS-CoV-2 virus infection. COVAXIN® has been studied in an ongoing 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.

Pharmacokinetic properties:

Evaluation of pharmacokinetic properties is not required for vaccines.

Preclinical safety data

All the formulations were tested for immunogenicity in mice, rats, and rabbits. Mice, rats, and rabbits were vaccinated on days 0, 7, and 14 (n+1 doses). Further, these formulations are tested for immunogenicity, safety, and protective efficacy in the Syrian Hamster challenge model and Non-Human Primates (Rhesus macaque) challenge model. The Hamsters were vaccinated on Days 0, 14, and 35 (n+1 doses), the live SARS-CoV-2 virus was challenged through the intranasal route on Day 50. Likewise, the Rhesus macaques were vaccinated on Days 0 and 14, and the live SARS- CoV-2 virus was challenged through intranasal and intratracheal routes on Day 28. All the formulations were found to be safe, immunogenic, and provided effective protection to both the upper and lower respiratory tract.[8]

6. PHARMACEUTICAL PARTICULARS

a. List of Excipients: Aluminium hydroxide gel, TLR7/8 Agonist, 2-Phenoxyethanol, Phosphate Buffered Saline
b. Incompatibilities: The vaccine should not be mixed with any other medicinal products or active immunizing agents.
c. 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.
d. 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.[8]

RESULTS

-Covaxin's Phase III trials, which began in November, last year, involved 25,800 participants aged between 18 and 98 across 25 sites. Over 2,000 participants (2,433) were over 60-year-old and 4,533 participants had co-morbidities. The trial is being called the largest clinical trial ever conducted in India. Trial stated that after 43 individuals from over 25,000 participants got COVID-19, the code was broken to see who got the vaccine and who got the placebo. In the placebo arm, there were 36 people who got the COVID-19 infection, whereas, in the vaccine arm there were only 7. Based on that, the calculation showed that

the vaccine efficacy is around 81 per cent. The interim result is very encouraging and it should put all sorts of doubts at rest and we should really look forward in terms of promoting this vaccine also in a big way as far as our national vaccine programme is concerned. We need to vaccinate a large number of people in our country to be able to prevent the pandemic from.

CONCLUSION –

India's first indigenous vaccine against COVID-19, Covaxin, is safe and generates immune response without any serious side effects, according to the interim results. The vaccine has also shown an interim efficacy of 81% in preventing Covid-19 during the phase-3 trial, which was conducted on 25,800 participants between 18-98 years of age, including 2,433 over the age of 60 and 4,500 with comorbidities. Research stated that BBV152 induced binding and neutralizing antibody responses & with the inclusion of the Algel-IMDG adjuvant, this is the first inactivated SARS-CoV-2 vaccine that has been reported to induce a Th1-biased response. The vaccine is being given to few lakhs of people, and there are hardly any serious side-effects. No death has been caused by Covaxin so far. Covaxin is a two-dose vaccine, with the second dose required to be given 28 days after the first one. So, India now self-sufficient in vaccine development and the developed vaccine Covaxin is effectively working to fight against coronavirus. Hoping in future to washout this deadly virus through the newly developed Indian weapon

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