Background document on the Bharat Biotech BBV152 COVAXIN® vaccine against COVID-19

Background document to the WHO Interim recommendations for use of the Bharat Biotech BBV152 COVAXIN® vaccine against COVID-19

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Note. This background document was developed to inform the initial recommendation-making process. It will not be updated on a regular basis. The latest Grade and ETR tables can be obtained here: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-bbv152-covaxin-annexes

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Background

This background document has been prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 vaccines to inform the discussions of SAGE at its meeting on 5 October 2021, which resulted in the issuance of the WHO Interim recommendations for use of the Bharat Biotech BBV152 COVAXIN® (COVID-19) vaccine.

Recommendations, annexes, and background document are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.
Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting webpage and SAGE Covid-19 Working Group webpage.

Context

The Bharat Biotech vaccine (BBV152) is a whole virion inactivated SARS-CoV-2 vaccine formulated with a imidazoquinoline class molecule (toll-like receptor (TLR) 7/8 agonist) (IMDG) adsorbed to alum (Algel-IMDG) (2). Inactivated vaccines platforms have been used for vaccine production for diseases such as seasonal influenza, polio, and pertussis. Inactivated vaccines cannot replicate, therefore cannot infect individuals. The IMDG and alum are adjuvants added to boost immunogenicity. Alum as an adjuvant supports a strong humoral response through neutralizing antibodies but has limited ability to induce a cell mediated response (3). A few animal studies of SARS-CoV-1 and MERS-CoV inactivated or vectored vaccines adjuvanted with alum have shown Th2 responses resulting in eosinophilic infiltration in the lungs (4, 5). A predominantly Th1 response is considered to have favourable antiviral properties (6). Therefore, IMDG, a novel vaccine adjuvant, which in animal studies and in phase 1 studies appears to weight the immune response to a Th1 response, was added to the BBV152 vaccine. The TLR 7/8 adjuvant IMDG has not been used in any other licensed vaccine.

Studies generally demonstrate that TLR 7/8 agonists enhance Th1 responses and inhibit Th2 responses. In addition, CD8 T-cell responses can also be increased in some cases when using TLR 7/8 agonists as adjuvants.

Characteristics of BBV152 (COVID-19) vaccine

Composition

The BHARAT BIOTECH COVID-19 vaccine (COVAXIN®, BBV152) includes the following ingredients: 6µg of whole-virion inactivated SARS-CoV-2 antigen (strain: NIV-2020-770, developed by β-propiolactone inactivation of an Indian strain of the novel coronavirus isolated by the Indian National Institute of Virology from an Italian tourist who tested positive for SARS CoV-2 (7)); and other inactive ingredients, such as aluminum hydroxide gel (250 µg); TLR 7/8 agonist (imidazoquinolinone class molecule) (15 µg); 2-phenoxyethanol, (2.5 mg); and phosphate buffer saline (≤0.5 ml), per dose.

Dosing regimen

BBV152 is administered as a 2-dose intramuscular injection (0.5 ml dose) given 4 weeks apart.

Stability and shelf-life

A shelf-life of 9 months is proposed. The vaccine is provided as a refrigerated suspension stored at 2–8 °C in a single-dose vial containing 10 doses (0.5 ml each). The vials should be protected from light. Unpunctured vials may be stored between 9–25 °C for up to 12 hours. After the first dose has been withdrawn, the vial should be held at 2–8 °C for up to 6 hours or at room temperature (maximally 25 °C) for up to 2 hours. The vial should be discarded if the vaccine is not used within these times.

Drug product description

The Bharat Biotech BBV152 (COVID-19) vaccine is a colourless to slightly yellow, clear to very opalescent sterile suspension for intramuscular injection.

Container

The vaccine is provided as a refrigerated suspension stored at 2–8 °C in a multidose vial containing 10 doses (0.5 ml each).

Pharmacokinetics

No biodistribution studies have been performed. Inactivated vaccines have been used for other antigens and do not replicate. The inactivation process is compliant with WHO standards.

Algel-IMDG was designed for targeted delivery of the vaccine antigen to lymph nodes without broad systemic circulation. In the lymph node, the TLR 7/8 agonist is released in the subcapsular sinus, leading to focused immune activation within the lymph node.

Developmental and reproductive toxicity

Animal developmental and reproductive toxicity (DART) studies are ongoing. A study using GLP was designed to investigate reproductive performance, embryonic and foetal development *in utero* and effect in neonates from birth until weaning. In top-line interim results, no test item-related effects were seen for does in-life, including at the injection site, for female reproduction, foetal survival or foetal physical development. There were no test item-related foetal external or visceral findings. The audited report including foetal skeletal development and post natal results are due later in 2021.

Preclinical studies

Preclinical studies were conducted in 5 animal species: mice, rats, rabbits, Syrian hamster, and non-human primates (Rhesus macaques). BBV152 vaccine formulations generated high antigen-binding and neutralizing

antibody titers, at both tested concentrations, in all mice, rats, and rabbits. No adverse events were observed after vaccination. The inactivated vaccine formulation containing TLR 7/8 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 responses (2). Further preclinical trials include 2 viral challenge studies: 1 in Syrian hamsters (8), and the other in non-human primates (9). In both studies the vaccine formulation with Algel-IMDG showed rapid virus clearance in lower respiratory tract with no sign of abnormal histopathological changes, while inducing robust immune response.

Clinical studies

The pivotal safety, efficacy and immunogenicity data informing registration of the vaccine are derived from five ongoing studies:

- Clinical Trial Registry – India (CTRI/2020/07/026300), a phase 1 trial in 375 adults (2-dose regimen: 3 mcg, 6 mcg, placebo).
- Clinical Trial Registry – India (CTRI/2020/07/026300), a phase 2 safety and immunogenicity trial in 380 adolescents and adults (2-dose regimen: 3 mcg, 6 mcg).
    - Phase 2 trial extension safety and immunogenicity study involving 190 adults (2-dose vs 2+1 regimens: 6 mcg + boost or placebo). Results are expected in the third quarter of 2021.
- Clinicaltrials.gov NCT04471519: "Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) for COVID-19 in Healthy Volunteers" (2-dose regimen: 6 mcg, placebo; protocol amendment to include booster dose 6 months after dose 2).
- Clinicaltrials.gov: NCT04641481, "An Efficacy and Safety Clinical Trial of an Investigational COVID-19 Vaccine (BBV152) in Adult Volunteers" (2-dose regimen involving 25 800 adults: 6 mcg, placebo).
- India (CTRI/2021/05/033752), Phase 2/3 Paediatric study safety and immunogenicity trial in children aged ≥2 to ≤18 years (2-dose regimen involving 525 children). The study was initiated May 21, 2021 and is ongoing.

The primary analysis of vaccine efficacy from the phase 3 trial is used within this background document as the main source of data.

Studies in other populations (e.g. pregnant women, people living with HIV, children with and without comorbidities) are also planned in the near future.

Immunogenicity studies in humans

The phase 1 trial showed seroconversion rates of 92% [95% CI: 80–94] in the 6 mcg with Algel-IMDG, 14 days post dose 2. Post 28 days after dose 2, geometric mean titres (GMTs) were 66 [95% CI: 53–82] in the 6 mcg Algel IMDG group based on MNT_{50} assay. 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 2-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 (10).

Three months after receipt of dose 2, follow-up serum samples were collected from the phase 1 study participants. In the 6 mcg group, GMTs (MNT_{50}) at day 104 were 70 [95% CI: 54–90.0]. Seroconversion based on MNT_{50} assay was reported in 76 participants (81% [95% CI: 71–88]) in the 6 mcg with Algel-IMDG group. This suggests that GMTs were maintained after 28 days post dose 2 and 104 days post dose 2. T-cell memory responses were also evaluated and found to be persistent among phase 1 vaccine recipients (11).

In the phase 2 trial, results in the 6 mcg Algel-IMDG group were similar to those in phase 1, with GMTs plaque reduction neutralization test ($PRNT_{50}$) of 0.1 [95% CI: 0.09–0.11] at day 0, 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 of 177 participants (98% [95% CI: 95–99]). GMTs (MNT_{50}) at day 56 were 160.1 [95% CI: 135.8–188.8]. Seroconversion based on MNT_{50} at day 56 was reported in 171 of 177 participants (97% [95% CI: 93–98]). IgG antibody titres (GMTs) to all epitopes (spike glycoprotein, receptor-binding domain, and nucleocapsid protein) were detected after the administration of the vaccine regimen. The Th1/Th2 cytokine ratio indicated bias to a Th1 cell response at day 42 (11).

The phase 3 study included a nested immunogenicity component for lot-to-lot consistency. GMTs measured using the SARS-CoV-2 microneutralization assay (MNT_{50}) in sera obtained at day 56, 4 weeks after the second vaccination showed lot-to-lot GMTs of 125.6 [95% CI: 111.2–141.8] in the vaccine group. GMTs in vaccinated individuals aged ≥18 to <60 years were 129.9 (95% CI 114.3-147.6); and in individuals aged ≥60 years, 101.2 [95% CI: 70.0–146.3]. By sex, GMTs in males were 118.2 [95% CI: 101.0–138.3); and in females, 138.4 (95% CI: 114.4–167.3) (1).

Immunogenicity studies against variants of concern

Neutralizing antibody titres ($PRNT_{50}$) of sera were collected (4 weeks after dose 2) from 38 vaccine recipients who had received the BBV152 vaccine candidate in the phase 2 trial and had no evidence of previous SARS CoV-2 infection. The sera were evaluated to determine the immunogenicity of the BBV152 vaccine candidate against the 3 different virus strains including the Alpha (B.1.1.7) variant of concern (VOC). A representative set of 20 serum samples of vaccine recipients were also tested to serve as comparison samples. Comparing the $PRNT_{50}$ values from these groups showed a non-significant difference ($P > 0.05$) in neutralization between the 3 tested strains (12).

Further immunogenicity studies were conducted as follows: 1 study reported neutralization antibodies in sera collected from patients post COVID-19 recovery (n=20); and vaccinees with 2 doses of BBV152 (n=17) against the Beta VOC (B.1.351) and Delta VOC (B.1.617.2). While there was a reduction in neutralization titres in sera of recovered COVID-19 cases (3.3-fold against Beta VOC; and 4.6-fold against Delta); and BBV152 vaccinees (3.0-fold against Beta; and 2.7 fold against Delta) (13). A second study 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 the neutralizing capacity against Delta VOC of sera of vaccinated individuals was similar to that of recovered COVID-19 cases (14). Another study was conducted to determine the IgG immune response and neutralizing activity of 19 convalescent sera specimens obtained from recovered cases of COVID-19 and confirmed for VOCs Alpha (n = 2) and Beta (n = 2). Additional virus mutations included the B1 lineage (D614G) (n=13) and B.1.1.28.2 (n=2). Testing was done 15–113 days post positive test result. The variants tested were compared with sera from 42 participants immunized with BBV152 as part of the phase 2 clinical trial (2 months post dose 2). This study found a high level of cross-neutralization in sera collected from variant infected individuals compared to those vaccinated with BBV152 (15).

Efficacy studies

The phase 3 study provides the primary analyses of this background paper based on a 2-dose regimen of BBV152 vaccine (1). It is an ongoing, multicentre, randomized, double-blind, placebo-controlled study, conducted in India, that assesses the efficacy, safety, and immunogenicity of a 2-dose regimen of BBV152 vaccine for the prevention of symptomatic COVID-19 in adults aged ≥18 years. The study is being conducted in 25 different sites. The initial study was conducted during a time when Delta variant was widely circulating. A total of 25 798 participants were randomized, of whom 24 419 were vaccinated with either 2 doses of BBV152 or placebo. The study included adults aged ≥18 years who were healthy or had stable medical conditions. Subgroups included varied by age (11% aged >60 years), by sex (33% women), and those with comorbidities (28.6%). The study enrolled participants at 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 contracted these variants of concern during the study period. 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 dose 1. This interim analysis included data up to 17 May 2021, and included a median of 146 days of safety data available after dose 1, and a median of 99 days of efficacy follow-up as of 2 weeks after dose 2.

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 receipt of dose 2. Of these cases, 24 occurred in the vaccinated group and 106 in the placebo group. The vaccine efficacy was found to be 78% [95% CI: 65–86%] against any severity COVID-19 disease. The vaccine efficacy among those with any severity COVID-19 infected with non-Delta variant SARS CoV-2 virus was 84% [95% CI: 71–93%]. Further analysis was conducted to look at secondary endpoints, including severe disease.

The study design included routine monthly PCR testing; therefore, the investigators were able to determine that efficacy against asymptomatic COVID-19 was 64% [95% CI: 29–82], with a total of 46 asymptomatic cases (13 in vaccine recipients and 33 in placebo recipients) (n=6289).

Participants will continue to be followed for 1 year for assessment of both safety and efficacy against COVID-19. Given the nature of the pandemic in India, Bharat Biotech unblinded prior to the agreed timelines. Placebo participants were offered BBV152.

Case definitions

Case definitions for symptomatic and severe COVID-19 are show in Box 1 and Box 2. Please note that the symptomatic case definition on which the data are reported, differs from the case definition in the study protocol initially submitted to WHO prequalification (see Annex 1 for details). Study endpoints are described in Box 3.

Box 1. Symptomatic COVID-19 case definition[a]

The **case definition for symptomatic COVID-19** was a SARS-CoV-2 positive RT-PCR nasopharyngeal swab, and at any time during the course of observation as per the phase 3 publication (1) was:

- **Any 1 of the following** new or worsening signs or symptoms:
  - Cough
  - Shortness of breath
  - Clinical or radiographic evidence of pneumonia.

OR

- **Any 2 of the following** new or worsening signs or symptoms:
  - Fever (≥38.0 °C)
  - Chills
  - Myalgia
  - Headache
  - Sore throat
  - A new olfactory or taste disorder.

Box 2. Severe COVID-19 case definition

The **case definition for severe COVID-19 disease** was: **virologically confirmed** (RT-PCR positive) SARS-CoV-2 severe respiratory tract infection with one or more of the following clinical manifestations:

1. Clinical signs at rest indicative of severe systemic illness (respiratory rate >30/min; heart rate >125/min; SpO2 <93%).
2. Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO)
3. Evidence of shock (SBP <90 mm Hg; DBP <60 mm Hg; or requiring vasopressors).