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

3 November 2021

World Health Organization

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).
4. Significant acute renal, hepatic, or neurologic dysfunction.
5. Admission to an ICU.
6. Death.

[a] The case definitions used in Box 1 were developed by the manufacturer and may differ from WHO standard definitions of COVID-19 disease severity which can be found in: COVID-19 Clinical management: living guidance (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1, accessed 3 October 2021).

Box 3. Primary and secondary efficacy and immunogenicity endpoints

Primary efficacy end points

- Symptomatic and severe COVID-19 cases.

Secondary efficacy end points

- Symptomatic COVID-19 cases.
- Severe symptomatic COVID-19 cases
- Any symptomatic COVID-19 cases in participants aged 18–59 years.
- Any symptomatic COVID-19 cases in participants aged ≥60 years.
- Any symptomatic COVID-19 cases in participants with a pre-existing medical condition.
- Asymptomatic COVID-19 cases.
- Any symptomatic and asymptomatic COVID-19 cases.
- COVID-19 deaths.
- All-cause mortality.
- Symptomatic COVID-19 including cases that were seropositive at baseline.
- Symptomatic or severe COVID-19 cases due to variants of concern.

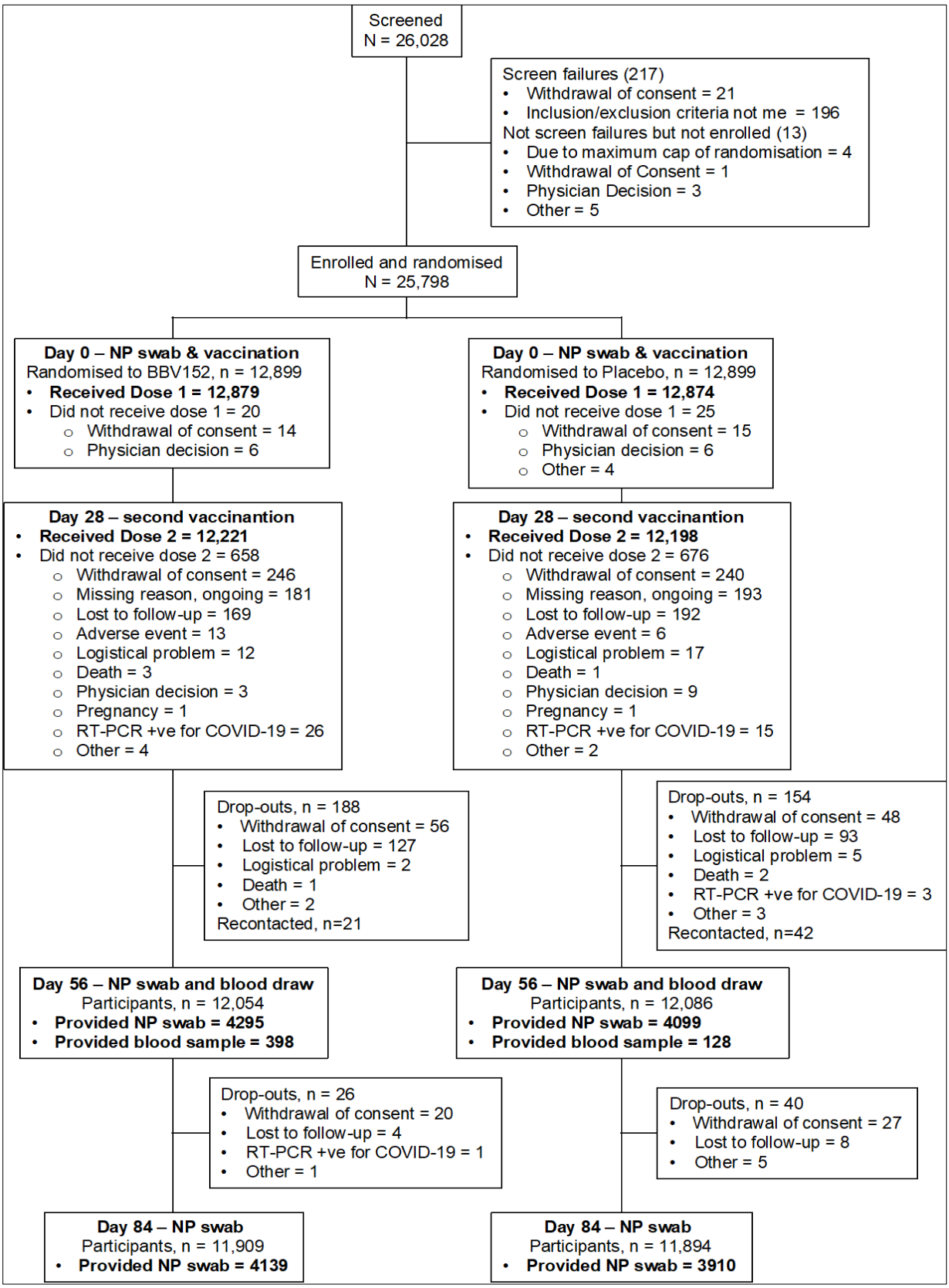
Secondary immunogenicity end points

- Geometric Mean Titre (GMT) of SARS-CoV-2 Specific nAb
- Geometric Mean Fold Rise (GMFR) of SARS-CoV-2 nAb
- GMT of SARS-CoV-2 S1 protein-specific binding antibody (bAb)
- Lot-to-lot consistency will be assessed based on the neutralizing titre of the 3 consistent lots used in the trial.

CONSORT diagram

The Consort diagram below (Figure 1) shows the number of study participants who were screened, enrolled as well as their allocation and testing over the course of the phase 3 trial.

Figure 1. Consort diagram



Participant characteristics

Table 1 provides a comparison of demographic characteristics among study participants by intervention (BBV152) versus placebo group.

Table 1. Demographic of participants in the safety population

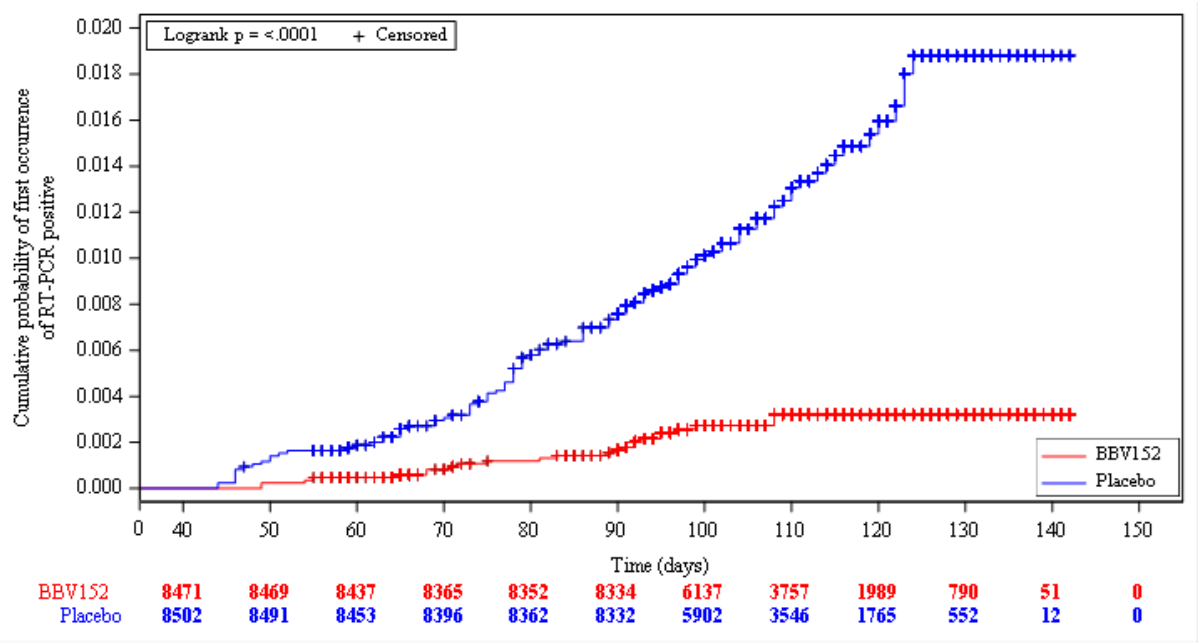
Parameter	**BBV152** n (%)	**Placebo** n (%)
Number of participants (n)	12 879	12 874
Age, years		
(Mean ± SD)	40·1 ± 13·8	40·1 ± 14·1
Range	18–92	18–97
Sex, n (%)		
Female	4214 (32·7)	4254 (33·0)
Male	8665 (67·3)	8620 (66·9)
Body Mass Index (BMI), kg/m^2		
	24·3 ± 4·4	24·3 ± 4·3
Pre-existing medical conditions, n (%)		
Stable cardiovascular disease	557 (4·3)	523 (4·1)
Stable respiratory disease	126 (1·0)	170 (1·3)
Controlled diabetes	706 (5·5)	735 (5·7)
Stable liver disease	25 (0·2)	28 (0·2)
Severe obesity (BMI >35)	56 (0·4)	94 (0·7)
Other stable comorbidities	839 (6·5)	910 (7·1)
Multiple risk categories	458 (3·6)	497 (3·9)
Baseline assessments for SARS-CoV-2 positivity*		
Positive for anti-SARS-CoV-2 IgG	3932 (30·5)	3886 (30·2)
Positive for SARS-CoV-2 by PCR	108 (0·8)	105 (0·8)

*At the screening or initial vaccination visit (visit 1) participants were evaluated for exposure to SARS-CoV-2 with both anti-SARS-CoV-2 IgG by ELISA and reverse-transcriptase polymerase chain reaction (PCR). Regardless of the outcome of these tests, participants were randomized and allocated to a group.

Efficacy against COVID-19

The phase 3 study demonstrated efficacy for the primary endpoint. A 2-dose regimen of BBV152 vaccine protected against symptomatic or severe COVID-19 in adults aged ≥18 years, including adults aged ≥60 years with an efficacy that was consistent across age groups but with some variability. The Kaplan Meier plot (Figure 2) provides the per protocol occurrence of confirmed symptomatic events (RT-PCR) for the study duration.

Figure 2. Kaplan Meier plot of first occurrence of virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 (per-protocol set) from day 0, events after day 42 (+14 days) after the second vaccination



Efficacy against severe COVID-19

In the per protocol analysis set, as of 14 days after vaccination, 1 vs 15 COVID-19 related severe cases (vaccine efficacy (VE) 93% [95% CI: 57–99]) were observed in the vaccinated group compared with the placebo group. The case splits for severe COVID-19 in the BBV152 group versus placebo group virtually eliminates the risk of vaccine-associated enhanced disease (VAED), consistent with the Th1 skewed immunologic response.

Efficacy in persons with previous SARS-CoV-2 infection (based on seropositivity at baseline)

A total of 48 participants in the vaccine group and 20 participants in the placebo group were seropositive for SARS CoV-2 IgG, at baseline. Both of these groups had higher MNT_{50} neutralizing antibody titres at day 56 than those participants who were seronegative at baseline (vaccinated participants MNT_{50} : 194.3 [95% CI: 134.4–280.9] vs placebo participants MNT_{50} : 27.4 [95% CI: 14.0–53.5]); (vaccinated participants MNT_{50} : 118.0 [95% CI: 104.0–134.0] vs placebo participants MNT_{50} : 11.9 [95% CI: 9.3–15.2]) respectively.

Efficacy against asymptomatic infections

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

Efficacy against new variants of concern

In the phase 3 study, newly emerging strains were detected in 79 of 16 973 samples (18 in the vaccine group, 61 in the placebo group) including Alpha, Beta, Delta, Kappa and Zeta. Overall 70.8% [95% CI: 50 – 84] vaccine

efficacy was noted against all variants. Among these, 50 cases (13 in the vaccine group, 37 in the placebo group) were due to Delta variant, resulting in a VE of 65% [95% CI: 33% – 83%]. Although no difference in neutralizing activity was shown between Alpha VOC and the original virus strain, there was a 1.9-fold reduction in the neutralizing titres against Zeta (B.1.1.28.2) when compared to the original virus strain. For the Delta VOC, there was a 2-fold reduction in neutralizing titres against B.1.617 compared to the original virus strain and a 3-fold reduction against Beta compared to original virus strain. No severe COVID-19 cases were reported in the vaccinee group; 4 severe cases were reported in the placebo group (Alpha, Delta, Kappa and unclassified).

Summary

Table 2 summarizes the vaccine efficacy results (1).

Table 2. Vaccine efficacy results from the BBV152 phase 3 clinical trials

Vaccine efficacy (VE) of first occurrence of symptomatic COVID-19 from phase 3 trial			
All participants included in analysis; onset of disease at least 14 days post dose 2			
Group/Subgroup	**BBV152/COVAXIN® Cases (N[a]) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE% (95% CI)**
All	24 (8471) 1507.46	106 (8502) 1478.20	78% (65–86)
All (except Delta variant related)	11 (8460) 1471.2	69 (8433) 1427.6	84% (71-93)
Sex			
Male	18 (5703) 1014.9	63 (5671) 985.5	72% (53–85)
Female	6 (2768) 492.5	43 (2831) 492.7	86% (67–95)
Age group (years)			
18–59	19 (7578) 1352.5	90 (7537) 1318.4	79% (66–88)
≥60	5 (893) 155.0	16 (965) 159.8	68% (8–91)
≥18 to 29	1 (2127)375.39	23 (2233)389.10	96% (72, 100)
≥30 to 39	6 (2383) 428.19	20 (2233) 392.87	73% (29, 91)
≥40 to 49	6 (1928) 344.88	23 (1877) 327.94	75% (37, 92)
≥50 to 59	6 (1140) 203.81	24 (1194) 208.50	74% (36, 91)
≥60 to 69	3 (639) 112.65	11 (685) 114.53	72% (-5, 95)
≥70 to 79	2 (223) 37.30	5 (244) 39.03	58% (-16, 96)
Subgroup analysis of participants			
Comorbidity, presence			
Yes	12 (2328) 371.9	37 (2518) 387.3	66% (34–84.)
No	12 (6562)	78 (6412)	85% (73–93)
Comorbidity, type			
Stable cardiovascular disease[b]	1 (347) 52.01	6 (338) 49.53	84 (-0.3–100)

Stable respiratory disease[c]	0 (86) 13.52	1 (127) 18.84	100 (-53–100)
Controlled diabetes[d]	0 (468) 69.35	12 (528) 7.99	100 (60.6–100)
Subgroup analysis of participants			
Regardless of baseline SARS- CoV-2 status	33 (12 879) 5089.6	115 (12 874) 5043.9	72% (58-81)
Vaccine efficacy in the **presence of variants of concern** of first occurrence of symptomatic COVID-19 with onset at least 14 days after dose 2			
	N=8471	N=8502	VE% (95% CI)
All variant related COVID-19	18 (8471) 2414.1	61 (8502) 2441.9	71% (50, 84)
Delta	13 (8471) 2442.3	37 (8502) 2416.3	65% (33–83)
Kappa	1	10	90% (30–99)
Alpha	1	3	Not calculated
Other[e]	3	11	73% (-2, 95)
Vaccine efficacy against **asymptomatic infection**			
All	13 (3248) 971.6	33 (3041) 897.5	64% (29–82)
Vaccine efficacy against **severe COVID-19** with onset at least 14 days after vaccination			
All	1 (8471) 2443.4	15 (8505) 2417.7	93% (57–99)
Vaccine efficacy against **symptomatic COVID-19 in participants with pre-existing medical conditions** with onset at least 14 days after vaccination			
	N=8471	N=8502	
All	12 (8471) 443.4	37 (8502) 419.7	67% (34–84)

[a] N = total number of participants at risk per category.
[b] Heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, hypertension and pulmonary hypertension.
[c] Emphysema and chronic bronchitis (idiopathic pulmonary fibrosis, and cystic fibrosis) or mild to moderate asthma.
[d] Type 1; Type 2.
[e] Other pangolin mutations detected include D614G (n=7); B.1.36 (n=3); B.1.1.419 (n=1); B.1.153 (n=1); B.1.351 and B.1.618 (n=1 each in placebo); and A (n=1).

Safety

Phase 3 safety findings

BBV152 vaccine demonstrated an acceptable safety and reactogenicity profile in adults aged ≥18 years, including adults aged ≥60 years (and 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.

Among the 25 798 participants who received BBV152 in the pivotal phase 3 study, the median follow-up after vaccination was 146 days; 23 803 (92.3%) participants had at least 2 months (8 weeks) of follow-up at the time of the published analysis.

In general, similar reactogenicity was observed in older adults compared to younger adults. Otherwise, no clinically relevant difference in the reactogenicity profile of BBV152 was observed by sex, comorbidity, SARS-CoV-2. Reactogenicity was demonstrated to be transient and most solicited adverse events (AEs) generally resolved in 1 to 2 days post vaccination.

The safety data included both solicited AEs, collected from the day of vaccination until 7 days afterwards; and unsolicited AEs, collected from the day of vaccination until 28 days afterwards. Data on medically attended adverse events (MAAEs), serious adverse events (SAEs) and deaths were collected from all 25 798 participants who received a study vaccination, and will continue to be collected for 1 year.

Frequencies of solicited and unsolicited adverse events

A total of 5959 AEs were reported by 3194 subjects, with a comparable proportion (12.4%) of subjects experiencing at least 1 AE in the BBV152 and placebo groups (Table 3). 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 SAEs 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 [0.5%] subjects) had a higher incidence of SAEs compared with the BBV152 group (39 [0.3%] subjects). One SAE (Immune thrombocytopenia) under the System Organ Class of "blood and lymphatic disorders" was considered related to BBV152 administration. There were 15 deaths during the study (5 in the vaccine group; 10 in placebo); none were considered by the Data Safety Monitoring Board to be related to BBV152 or placebo; 6 deaths across both groups were reported to be related to COVID-19. The 5 deaths in the BBV152 group were all due to causes unrelated to vaccination and included haemorrhagic stroke, metastatic ovarian cancer, cardiac arrest, COVID-19, and sudden cardiac arrest/intracranial haemorrhage (unconfirmed). The 10 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; 5 deaths were from COVID 19; 1 death with unknown cause and symptoms of headache; and 2 deaths which remain to be determined.

No anaphylactic events or cases of Guillain Barré Syndrome were reported.

Approximately 9% of subjects experienced at least 1 solicited AE within 7 days post vaccination. Overall incidence rates of solicited AEs 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 AEs, only local injection pain was reported with an incidence >1% after either 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 dose 1, falling to 1.81% and 1.62% subjects respectively after dose 2. Other frequently reported local AEs 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 AEs were reported less frequently: in 2.6% and 1.9% subjects after dose 1; and in 1.8% and 1.6% subjects after dose 2 in the BBV152 and placebo groups, respectively (Table 4). The most frequent solicited

systemic AE overall was headache, followed by pyrexia, fatigue and myalgia; all with incidences <1% in both groups. A total of 767 unsolicited AEs were reported in 450 subjects: 1.76% in the BBV152 group; and 1.7% in the placebo group. All unsolicited AEs 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 (within 30 minutes) AEs were observed in only 0.1% of subjects post dose 1; and 0.1% of subjects post dose 2. A higher number of immediate (within 30 minutes) AEs post-dose were observed in the placebo group (29 events, 23 subjects) compared with the BBV152 group (14 events, 12 subjects); most of these immediate AEs occurred post dose 1. The proportion of subjects experiencing any MAAEs and Adverse Events of Special Interest (AESIs) was comparable between the BBV152 and placebo groups. Adverse events led to discontinuation of study intervention in 19 subjects overall: 13 in the BBV152 group, and 6 in the placebo group. Overall, BBV152 exhibited a good reactogenicity profile with similar rates of solicited, unsolicited, and serious adverse events, and AESIs in BBV152 and placebo groups.

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 55 857 038 doses of BBV152, there were no potential thromboembolic events reported through the CO-WIN platform (16).

Special considerations

Pregnancy

Participants were excluded if they were pregnant or planned to become pregnant within 3 months of vaccine administration. Pregnancy was reported for 2 subjects: 1 in the vaccine group and 1 in the control group. These 2 participants continue to be followed.

A developmental reproductive toxicity study of BBV152 has not been completed as yet. A pregnancy sub-study is planned and the Government of India is planning a pregnancy registry.

Breastfeeding

It is unknown whether the vaccine is excreted in human milk.

Paediatric population

The phase 2 trial enrolled a limited number of participants (n=14) aged between 12 and 18 years. Seroconversion and GMTs across these age groups were comparable to adults aged between 18 and 60 years. An additional immunogenicity and safety trial is underway in subjects aged <18 years.

Immunosuppression

No data are currently available in immunocompromised subjects, including those receiving immunosuppressant therapy. The efficacy of the vaccine may be lower in immunosuppressed individuals.

Safety related to vaccine interactions

No data are available on use of the vaccine with concomitant vaccines, including influenza vaccines. Licensed seasonal influenza and pneumococcal vaccinations were permitted at least 7 days before or after the study vaccine.

Table 3. Summary of adverse events from the BBV152 phase 3 trial

	BBV152 (N = 12 879)		**Placebo** (N = 12 874)		**Total** (N = 25 798)	
	Events n	Participants n (%)	Events n	Participants n (%)	Events n	Participants n (%)
All adverse events (AEs)	2930	1597 (12·4)	3029	1597 (12·4)	5959	3194 (12·4)
Solicited adverse events						
Any solicited AE	1949	1223 (9·5)	1720	1136 (8·8)	3669	2359 (9·2)
Solicited AE within 7 days post dose 1	1151	809 (6·3)	994	702 (5·5)	2145	151 (5·9)
Solicited AE within 7 days post dose 2	798	568 (4·4)	726	548 (4·3)	1524	1116 (4·3)
Unsolicited adverse events	981	489 (3·8)	1309	609 (4·7)	2290	1098 (4·3)
Serious adverse events	40	39 (0·30)	66	60 (0·47)	106	99 (0·38)
All medically attended adverse events (MAAEs)	475	301 (2·3)	548	319 (2·5)	1023	620 (2·4)
Immediate AEs (within 30 mins post vaccination)						
Any immediate AE	14	12 (0·10)	29	23 (0·18)	43	35 (0·14)
Immediate AEs post dose 1	11	10 (0·08)	19	17 (0·13)	30	27 (0·10)
Immediate AEs post dose 2	3	3 (0·02)	10	8 (0·06)	13	11 (0·04)
All adverse events of special interest (AESI)	23	23 (0·18)	23	23 (0·18)	46	46 (0·18)
All ongoing AEs	63	41 (0·32)	93	59 (0·46)	156	100 (0·39)

N = number of participants in the relevant population,
Events: n = number of individual events reported (1 participant may have reported several AEs),
Participants: n = number of participants reporting at least one event,
% = number of participants with an event/N*100

Table 4. Incidence of solicited adverse events after each dose of BBV152 vaccine, phases 1, 2 and 3 combined

Participants reporting solicited adverse events (AEs) within 7 days of vaccination	**Phases 1, 2 and 3**					
	BBV152		**Placebo**		**Total**	
	13169		12949		26118	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Any local AE	502 (4%)	302 (2%)	448 (3%)	268 (2%)	950 (4%)	570 (2%)
Pain	414 (3%)	249 (2%)	362 (3%)	209 (2%)	776 (3%)	458 (2%)
Erythema	35 (1%)	21 (0.1%)	26 (0.2%)	25 (0.2%)	61 (0.2%)	46 (0.2%)
Induration	32 (0.2%)	18 (0.1%)	26 (0.2%)	18 (0.1%)	58 (0.2%)	36 (0.1%)
Swelling	21 (0.2%)	14 (0.1%)	34 (0.3%)	16 (0.1%)	55 (0.2%)	30 (0.1%)
Any systematic AE	459 (4%)	308 (2%)	334 (3%)	249 (2%)	793 (3%)	557 (2%)
Pyrexia	128 (1%)	95 (0.7%)	81 (0.6%)	80 (0.6%)	209 (0.8%)	175 (0.7%)
Fatigue	59 (0.5%)	41 (0.3%)	41 (0.3%)	20 (0.2%)	100 (0.4%)	61 (0.2%)
Chills	28 (0.2%)	9 (0.1%)	22 (0.2%)	16 (0.1%)	50 (0.2%)	25 (0.1%)
Headache	140 (1.1%)	92 (0.7%)	121 (0.9%)	70 (0.5%)	261 (1%)	162 (0.6%)
Myalgia	54 (0.4%)	39 (0.3%)	28 (0.2%)	28 (0.2%)	82 (0.3%)	67 (0.3%)
Arthralgia	17 (0.1%)	12 (0.1%)	17 (0.1%)	17 (0.1%)	34 (0.1%)	29 (0.1%)
Nausea	20 (0.2%)	14 (0.1%)	15 (0.1%)	10 (0.1%)	35 (0.1%)	24 (0.1%)
Vomiting	13 (0.1%)	6 (0.1%)	9 (0.1%)	8 (0.1%)	22 (0.1%)	14 (0.1%)
SAE	15 (0.1%)	25 (0.2%)	6 (0.1%)	60 (0.5%)	21 (0.1%)	85 (0.3%)

Post licensure studies

BBV152 has been licensed for use in 23 countries globally; however roll-out has been limited mostly to India where over 77 million doses have been distributed and used. Vaccine effectiveness studies are being conducted in India, and results will be available in the coming months.

A company document submitted to WHO contains the following text (quoted):
"The Indian Council of Medical Research and Ministry of Health and Family Welfare, Government of India have developed India COVID-19 vaccine tracker to make available vaccine effectiveness data against mortality, in public domain. For developing this tracker, ICMR has analysed effectiveness of 1 and 2 doses of COVAXIN against mortality. Data were analysed for a 3-month period (18 April to 18 July 2021) and analysis was done for 8 608 635 726 person week time in unvaccinated, 144 164 638 persons week time for those vaccinated with a single dose and 95 119 742 persons week time for two dose vaccination. Effectiveness of single COVAXIN vaccine dose was 90% and for 2 doses was 96% against mortality" (17).

It is hoped that these data, provided to the prequalification team at WHO, will be made publicly available along with methods for deriving the estimates.

Finally, a small study conducted in a convenience sample of health workers who received the BBV152 vaccine, between February 2021 and May 2021, at a vaccination care centre in India provides supporting evidence for the effectiveness only 1 dose of BBV152 vaccine for individuals who have been previously infected with SARS-CoV-2. Prior infection with SARS-CoV-2 was determined by SARS-CoV-2 IgG positivity before receipt of dose 1. A total of 84 individuals had no previous evidence of SARS-CoV-2 infection; 30 had evidence of previous infection. This latter group showed similar antibody levels after 1 dose as naïve individuals after 2 doses. This study suggests that for individuals who have had SARS-CoV-2 infection, 1 dose of BBV152 vaccine could provide similar antibody protection as 2 doses (18).

Further post marketing studies are anticipated in the coming months.

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Annex 1: Case definition from the phase 3 protocol as submitted to WHO pre-qualification team

The case definitions below are from the phase 3 protocol as submitted to WHO pre-qualification team. The efficacy data presented in this background document are from peer-reviewed publications as listed in the reference section above.

COVID-19 cases included participants who met any of the two below following criteria:

- Case definition for primary efficacy symptomatic endpoint
- Case definition for severe symptomatic COVID-19

Any one of the below-mentioned criteria (A or B) described in Table A1 must be met, along with a positive SARS-CoV-2 RT-PCR of a confirmed symptomatic case.

Table A1. Case definitions from phase 3 protocol

Criteria A: **One or more**	**OR**	Criteria B: **Two or more**
1. Shortness of breath/difficulty in breathing 2. New-onset anosmia/aguesia 3. Oxygen saturation of <94% or escalation by requiring supplemental oxygen. 4. Pneumonia: diagnosed by chest X-ray or CT scan 5. Evidence of shock 6. ICU admission/death		1. Fever 2. Chills 3. New cough 4. Myalgia/fatigue 5. Headache 6. Sore throat 7. Nausea/vomiting 8. Diarrhoea 9. Congestion/runny nose
AND		
Positive SARS-CoV-2 RT-PCR test		

WHO reference number: WHO/2019-nCoV/vaccines/SAGE_recommendation/BBV152/background/2021.1