Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Is vaccination with BBV152 (Covaxin/Bharat) effective and safe in the prevention of COVID-19 infections?: A Rapid Review

Review by: Christdianzen Grace Saroca, MD, Marie Carmela Lapitan, MD

RECOMMENDATIONS

1. **We recommend the use of BBV152 (Covaxin/Bharat), 0.5 mL/dose, in a two-dose regimen, 28 days apart for the prevention of symptomatic COVID-19 infection in healthy adults**. *(Moderate quality of evidence; Strong recommendation)*

2. **We suggest the use of BBV152 (Covaxin/Bharat), 0.5 mL/dose, in a two-dose regimen, 28 days apart for the prevention of symptomatic COVID-19 infection**:
   a. Adults who have stable medical co-morbidities and are at high risk for severe infection *(Low quality of evidence; Weak recommendation)*
   b. Healthy, older adults (>60 years old) *(Low quality of evidence; Weak recommendation)*
   c. Pregnant and lactating women, after discussing with a physician *(No direct evidence; Weak recommendation)*
   d. Immunocompromised patients, after discussing with a physician *(No direct evidence; Weak recommendation)*

3. **We suggest against the use of BBV152 (Covaxin/Bharat) for the prevention of COVID-19 in children and adolescents**. *(No evidence; Weak recommendation)*

4. **We recommend against the use of BBV152 (Covaxin/Bharat) in individuals who have known allergies to its contents/excipients**. *(Best practice statement)*

(*Note: The recommendation regarding the use of BBV152 in the context of the Delta variant is included in the Delta variant review)*

Key Findings

The search performed on September 20, 2021 included one (1) randomized controlled clinical trial (RCT) (n=25,798) and seven (7) observational studies, which provided evidence on the efficacy, effectiveness, and safety of BBV152 (Covaxin/Bharat) in the prevention of SARS-CoV-2 infection, including those due to the variants of concern.

Introduction

In the effort against the COVID-19 pandemic, equal worldwide distribution of safe and effective vaccines is key. As India has had the second highest number of COVID-19 infections, Bharat Biotech and the Indian Council of Medical Research developed the BBV152 vaccine (Covaxin®), which was approved for emergency use in the country on January 3, 2021.[1] BBV152 was produced from the virus strain (NIV-2020-770) with the Asp614Gly mutation isolated and sequenced from a patient infected with COVID-19. This whole virion βpropiolactone-inactivated SARS-CoV-2 vaccine with a

toll-like receptor 7/8 agonist molecule absorbed to alum (Algel-IMDG) leads to a Th1 response. It is a liquid suspension given intramuscularly at 0.5 mL/dose, in a two-dose regimen, 28 days apart.[2] BBV152 has no reconstitution requirement, needing only refrigerator storage at 2 to 8˚C with a shelf life of approximately 2 years.[1]

In order to aid future decisions for vaccine procurement, this review was done on the clinical efficacy, effectiveness, and safety of BBV152 (Covaxin/Bharat).

Review Methods

General Search Results

As of September 20, 2021, eight (8) studies were included in this review. Only one (1) was a randomized controlled trial (RCT), which investigated the efficacy of BBV152 compared to placebo, while four (4) were observational studies. Two (2) were case series of adverse events, and one (1) was a review that cited safety reports. Two (2) reported on effectiveness on variants. Several reports were also identified in the search that mentioned the use of BBV152 but were excluded in this review because BBV152 was used in a very small minority of the study population and no separate results were presented for the subgroup.

Results

CLINICAL EFFICACY

A double-blind, randomized, controlled Phase 3 trial is currently being conducted in 25 Indian hospitals to evaluate the overall vaccine efficacy (VE) after two doses of BBV152 compared with placebo in preventing COVID-19 infection among participants who were seronegative at baseline. After a median follow up of 146 days, VE for the prevention of symptomatic COVID-19 infection was 77.8% (95% CI 65.2-86.4) at 2 weeks post 2nd dose. Vaccine efficacy was 93.4% (95% CI 57.1-99.8) against severe disease and 63.6% (95% CI 29-82.4) for asymptomatic infection. VE for symptomatic COVID-19 infection among those at least 60 years of age was 67.8% (95% CI 8-90).[3]

The characteristics of this included trial are presented in Appendix 2 while the risk of bias assessment is presented in Appendix 3.

Summary of findings and GRADE profile on BBV152 efficacy is presented in Appendix 6.

REAL WORLD EVIDENCE: EFFECTIVENESS

General Population

While reports on vaccine breakthrough infection of COVID-19 exists, all involved multiple vaccines and BBV152 was used in a minority of the study population. As no separate reporting of the outcomes of interest were given per vaccine type, clear information on BBV152 effectiveness could not be extracted in the studies identified in the search.

Health Care Workers

The cross-sectional Coronavirus Vaccine-induced Antibody Titre (COVAT) study assessed the outcomes of 93 health care workers (HCWs) who received two doses of BBV152. In this study, at Days 21-36 after the second dose, the breakthrough infection rate was recorded at 2.2%. All of which were mild cases and all recovered.[4]

Clinical Efficacy and Effectiveness on Special Populations of Interest (older persons, children, immunocompromised, and pregnant women)
No study was identified on the real-world evidence on BBV152 on older persons, the immunocompromised, children or pregnant women.

SAFETY
Regulatory Clinical Trial Evidence
In the Phase 3 trial, after a median follow up of 146 days after the first dose for 93% of the study population, five (5) deaths in the BBV152 recipients and ten (10) in those who received the placebo were reported. All causes were assessed to be unrelated to the vaccination. Deaths in the BBV152 group were due to cerebellar hemorrhage, hemorrhagic stroke, ovarian cancer with metastases, sudden cardiac death, and COVID-19 infection. Meanwhile, the causes of death in the placebo group included alcohol overdose, myocardial infarction, cardiac arrest with underlying hypertension, COVID 19, and two (2) from yet undetermined causes.[3]

Only local injection pain had an incidence greater than 1% among the local solicited adverse events. The most frequent solicited systemic adverse event was headache, which occurred in less than 1% in both groups. Apart from a lower incidence of adverse events after the second dose compared to the first, and being slightly higher in the BBV152 group compared to the placebo, there were no significant differences observed in solicited, unsolicited, and serious adverse events rates in the two treatment groups. No anaphylactic events were noted. Long-term safety outcomes are still underway.[3]

Summary of findings and GRADE profile on BBV152 safety is presented in Appendix 7.

REAL WORLD EVIDENCE: SAFETY
In the cross-sectional COVAT study that included healthcare workers who received two (2) doses of BBV152, 11.1% (10/90) were reported to have mild to moderate side effects. No serious solicited or unsolicited side effects were noted. When compared with ChAdOx1 recipients in the same study, BBV152 recipients reported less adverse events.[4]

The characteristics and detailed results of this trial are presented in Appendix 4.

Reports on Adverse Events of Interest
Immune thrombocytopenic purpura (ITP) in a SARS-CoV-2 seropositive participant at baseline was reported as a possible related serious adverse event in one (1) patient in the BBV152 group in the regulatory trial. The event occurred 39 days after the second dose and resolved in four (4) days.[3]

In the National AEFI Committee report to the Union Health Ministry of India, of more than 2,300 adverse events, as cited in the review by Rajpurohit et. al, no potential thromboembolic events following BBV152 administration was included.[5]

Other Reported Adverse Events
One (1) case report documented a 60-year-old diabetic and hypertensive who developed herpes zoster four (4) days after receiving BBV152.[6] Another case report documented a 34-year-old woman developing new-onset subacute thyroiditis after receiving the first dose of BBV152.[7]

Effectiveness Against Variants of Concern

Alpha

One (1) study showed a 1.4-fold reduction in the titers with the Alpha-variant compared to the B.1 strain in the sera of BBV152 vaccinees, although the confidence intervals were overlapping [8] Another study showed no significant difference in the neutralizing antibody titers with the Alpha strain compared with the hCOV19/India/20-20770 and the hCoV-19/India/202Q11 from the BBV152 sera.[9]

Beta

Two (2) studies showed a 3-fold reduction in antibody neutralization after Beta-variant infection, compared with the reference strain, among BBV152 vaccine recipients.[8,10]

Delta

The same two (2) studies above also reported reduced immune response after Delta-variant infection among BBV152 vaccine recipients, but at a slightly lesser degree compared to the Beta-variant. The declines were 2.7-fold [10] and 2.9-fold.[8]

In addition, the regulatory trial reported a vaccine efficacy of 65.2% (95% CI 33.1–83.0) among the 50 Delta-variant positive confirmed cases. It also showed significantly lower viral loads among the breakthrough symptomatic infection cases in the vaccine versus placebo groups.[3]

Gamma

No study was identified that investigated on the effect of BBV152 vaccine against the Gamma-variant.

Appendix 5 presents the characteristics and the details of the studies on the performance of the BBV152 vaccine against variants of concern.

HETEROLOGOUS VACCINATION

One (1) study reported on the outcomes of BBV152 in a heterologous vaccination regimen. In Uttar Pradesh, India, a group of individuals were inadvertently given ChAdOx1 (Covishield) followed by BBV152 after an interval of six (6) weeks.[8] Immunologic responses showed that IgG and neutralizing antibody titers of the heterologous group were significantly higher when compared to those who received the homologous ChAdOx1-ChAdOx1 and homologous BBV152-BBV152 regimen.[8] Heterologous vaccination was also noted to produce higher antibody titers against the variants of concern (Alpha, Beta, and Delta) compared to homologous BBV152 vaccination, with heterologous titers at 3-fold higher levels.[8]

In the same study, no serious adverse events were reported following immunization with the heterologous regimen. The most common local adverse event in all groups was pain at injection site, while the most common systemic adverse events were fever and malaise. Overall, the adverse event frequency in the heterologous group was similar to that in the homologous groups.

Authorizations

The Philippine FDA granted emergency use authorization for BBV152 (Covaxin/Bharat) on June 21, 2021.[11]

As of September 27, 2021, the application for WHO emergency use listing is still under process.

Ongoing Trials

The search performed on September 7, 2021 of the Clinicaltrials.gov registry showed four (4) ongoing trials.

Appendix 8 presents the details of the ongoing trials of BBV152.

Research Gaps

Research gaps regarding BBV152 vaccination for COVID-19 infection prevention include its efficacy, effectiveness, and safety in special populations such as the older and very old patients, children, and immunocompromised populations. Other gaps identified are the duration of protection, long term efficacy or effectiveness, and long-term safety of the vaccine. Lastly, the clinical efficacy or effectiveness and safety of heterologous vaccination as well as its clinical efficacy or effectiveness against infection with variants of concern are also identified research gaps.

References

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[11] Philippine Food and Drug Administration. Emergency Use Authorization (EUA) for Whole Virion, Inactivated Corona Virus Vaccine [Covaxin] [Internet]. [cited 2021 Sep 20]. Available from: https://www.fda.gov.ph/wp-content/uploads/2021/06/EUA-Bharat-website.pdf

Excluded Studies

The following studies were not included in the evidence summary with the reasons as stated:

Study Title	Reason for Exclusion
Sapkal et. al. "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"	Discussed effect on variant under investigation only
Sapkal, et. al. "Neutralization of B.1.1.28 P2 variant with sera of natural SARS-CoV-2 infection and recipients of BBV152 vaccine"	Discussed effect on variant under investigation only
Ghosh et al "Genomic profiles of vaccine breakthrough SARS-CoV-2 strains from Odisha, India" - MedRxiv	Covaxin only given to a minority of the population, no usable outcome.
R Pandurangaiah et al. "Post vaccination COVID-19 infection among health care workers in secondary medical care centre" - International Journal of Clinical Obstetrics and Gynaecology	Covaxin only give to a minority of the population, no subgroup analysis
Sharma et. Al. "Breakthrough infection with SARS-CoV-2 and its predictors among healthcare workers in a medical college and hospital complex in Delhi, India"	Covaxin only given to a minority of the population, no subgroup analysis
Tyagi et. al. "Breakthrough COVID19 infections after vaccinations in healthcare and other workers in a chronic care medical facility in New Delhi, India" - Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2021	Covaxin only given to a minority of the population, no subgroup analysis
Farinholt et. al. "Transmission event of SARS-COV-2 Delta variant reveals multiple vaccine breakthrough infections" - MedRxiv July 12, 2021"	Covaxin only given to a minority of the population, no subgroup analysis
Cherian et. al. "Safety of the ChAdOx1 nCoV-19 and the BBV152 vaccines in 724 patients with rheumatic diseases: a post-vaccination cross-sectional survey"	Covaxin only given to a minority of the population, no subgroup analysis
Dash et. al. "Breakthrough SARS-CoV-2 infections in an eastern state of India: A preliminary report" - Research Square 2021	Covaxin only given to a minority of the population, no subgroup analysis
Guha et. al. "The incidence and in-hospital mortality of COVID-19 patients post-vaccination in eastern India" – MedRxiv July 22, 2021	Covaxin only given to a minority of the population, no event of interest reported with Covaxin
Shenoy et. al. "Immunogenicity of the ChAdOx1 nCoV-19 and the BBV152 Vaccines in Patients with Autoimmune Rheumatic Diseases"	Covaxin only given to a minority of the population, no event of interest reported with Covaxin
Singh Awadhesh Kumar Singh et. al. "Antibody Response after First-dose of ChAdOx1 nCov-19 and BBV-152 Health Care Workers in India: Preliminiary Results of Cross-Sectional Coronavirus Vaccine-induced Antibody Titre (COVAT) study" - MedRxiv. April 13, 2021	Covaxin only given to a minority of the population, no subgroup analysis for outcomes of interest

Appendix 1. Evidence to Decision

Table 1. Summary of Initial Judgements Prior to Panel Discussion (N = 9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					
Benefits	Large (5)	Moderate (4)	Small	Uncertain			• VE 93.4% (95% CI 57.1-99.8) against severe disease and 63.6% (95% CI 29-82.4) for asymptomatic infection. • VE for symptomatic COVID-19 infection among those at least 60 years of age was 67.8% (95% CI 8-90).
Harm	Large	Small (8)	Uncertain (1)				• Only local injection pain had an incidence greater than 1% among the local solicited adverse events. • Long-term safety outcomes are still underway.
Certainty of evidence	High (1)	Moderate (3)	Low (5)	Very Low			• Very low to moderate
Balance of effects	Favors vaccine (9)	Does not favor vaccine	Uncertain				
Values	Important uncertainty or variability	Possibly important uncertainty or variability (4)	Possibly no important uncertainty or variability (3)	No important uncertainty or variability (2)			
Resources required	Uncertain	Large cost	Moderate cost (7)	Negligible cost or savings (1)	Moderate savings	Large savings (1)	• A single dose of Covaxin would cost around $14 (approximately PHP 710). Two doses are needed per individual. No reconstitution requirement, needing only refrigerator storage at 2 to 8˚C and has a shelf life of approximately 2 years.

Certainty of evidence of resources required	No included studies (7)	Very low (1)	Low (1)	Moderate	High		
Cost effectiveness	No included studies (8)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (6)	Reduced	Probably no impact (2)	Increased (1)			
Acceptability	Uncertain (6)	No	Yes (3)				
Feasibility	Uncertain (1)	No	Yes (8)				

Appendix 2. Characteristics of the Randomized Controlled Trial (Ph3) on the Efficacy and Safety of Covaxin

Trial Identifier	**NCT04641481**
Vaccine	**BBV152 (Covaxin)**
Data Sources	Ella et. Al., "Efficacy, safety, and lot to lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): A, double-blind, randomised, controlled phase 3 trial. MedRxiv 2021. https://doi.org/10.1101/2021.06.30.21259439
POPULATION	
Total Randomized	25,798 (16,973 per protocol, excluding seropositives)
Inclusions	
● Age	18 to 99 years old
● Race/ Ethnicity	Indian
● Immunocompromised	Excluded
● Pregnant and breastfeeding	Excluded
● With concomitant comorbidities	Participants with good general health as determined by the discretion of the investigator, or participants with stable medical conditions. A stable medical condition is defined as a disease not requiring significant change in therapy or hospitalization or worsening disease during the 3 months before enrolment.
● With previous COVID infection	Excluded
● With known previous exposure to COVID	Excluded
● Seropositive at baseline	(30%) Excluded in per protocol analysis but included at safety dataset

Exclusions	• History of any other COVID-19 investigational or licensed vaccination • Known history of SARS-CoV-2 infection, as declared by the subject • For women, positive urine pregnancy test before the first dose of vaccination or any time during the study period • Temperature >38.0°C (100.4°F) or symptoms of an acute self-limited illness such as an upper respiratory infection or gastroenteritis within three days prior to each dose of vaccine • Resident of COVID-19 infection in the same household • Known case of HIV, hepatitis B, or hepatitis C infection • Receipt of any licensed/experimental vaccine within four weeks before enrolment in this study • Receipt of immunoglobulin or other blood products within the three months before vaccination in this study • Immunosuppression as a result of an underlying illness or treatment with immunosuppressive or cytotoxic drugs, or use of anticancer chemotherapy or radiation therapy within the preceding 36 months • Immunoglobulins, anti-cytokine antibodies, and blood products within 6 months prior to study vaccination, during, and 21 days following the last dose of vaccination • Pregnancy, lactation, or willingness/intention to become pregnant during the first 6 months after enrolment • Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, an endocrine disorder, and neurological illness (mild/moderate well-controlled comorbidities are allowed)
INTERVENTION (VACCINE)	
Type	Whole-virion ß-propiolactone-inactivated SARS-CoV-2 vaccine
Active substance	BBV152 (6µg virus antigen-Algel - Imidazoquinoline)
Storage and Cold Chain Considerations	
● Shipping and transport	Supplied and stored in single use glass vials, with no on site dose preparation necessary
● Storage and shelf life prior to dilution/ opening	2 to 8°C, approximately 2 years
● Storage and shelf-life after dilution/opening	28 days
Final product	
Form and use	Liquid suspension
Excipients	N/A
Trial-specific considerations	
Dosing and administration	0.5 mL/vial on days 0 and 28
Number randomized	12,879

COMPARATOR	
Type, dosing and administration	Phosphate buffered saline with Alum (without antigen), 0.5 mL
Number randomized	12,874
ACTUAL VACCINATION INTERVAL	28 days
OUTCOMES	Based on per protocol population including randomly assigned participants who were seronegative at baseline and received two doses of either vaccine or placebo, and remained on study at least 14 days after their second dose with no previous virologically-confirmed SARS-CoV-2 infection [Time Frame: Day 42 to Month 12]
Primary efficacy endpoints	RT-PCR positive symptomatic cases of COVID-19 with onset at least 14 days after 2nd dose: **77.8% vaccine efficacy (95% CI 65.2–86.4)**
Primary safety endpoints	None
Secondary endpoints	• RT-PCR positive Severe Symptomatic COVID-19 cases: vaccine efficacy of **93.4% (95% CI: 57.1–99.8)** • RT-PCR positive symptomatic COVID-19 cases 18-59 years of age: **79.4% (66.0–88.2)** • RT-PCR positive symptomatic COVID-19 cases 60 years of age or older: efficacy of **67.8% (8.0–90.0)** • RT-PCR positive COVID-19 asymptomatic and symptomatic cases occurring from two weeks after the second vaccination • Immunogenicity: Lot-to-Lot consistency of three consecutive GMP Lots [Time Frame: Day 0 to Day 42] Assessed based Wild-type SARS-CoV-2 Specific Neutralizing Antibody (nAb) • Geometric Mean Titer (GMT) of SARS-CoV-2 Specific Neutralizing Antibody (nAb) [Time Frame: Day 0 to Month 12] Specific Neutralizing Antibody (nAb • Reactogenicity and Safety [Time Frame: Day 42 to Month 12] Solicited, Unsolicited, Serious Adverse Events
Subgroups considered in the analysis	
● Age	18-59 years, 60 or older (10.7%)
● Sex	Female, Male
● Ethnic groups	N/A
● Baseline seropositivity status / evidence of previous infection	Positive for anti-SARS-CoV-2 IgG, 30% seropositive at baseline excluded from per protocol analysis but contributed to safety dataset
● Medical comorbidities	Stable cardiovascular disease, stable respiratory disease, controlled diabetes, stable liver disease, severe obesity (BMI>35), other stable comorbidities, multiple risk categories
● Immunocompromised /HIV disease	Excluded
● Risk for acquiring COVID infection	Participants considered to be at-risk of acquiring COVID-19 were prioritized, so a total of 2,750 participants were above 60 years of age and 7,065 reported at least one pre-existing medical condition across ages

● Risk for progression to severe COVID	N/A
● Dosing regimen	N/A
Follow up	
● Planned	Day 42 to Month 12
● At data cutoff of interim report (first interim analysis)	Day 56 (1 month after second dose) Median of 146 days after first dose (92.3%)
Date of Data Cut-off date for latest available trial data	May 17, 2021 ß
METHODS / OTHER TRIAL PARAMETERS	
Blinding	Participants, investigators, study coordinators, study-related personnel, sponsor, and study nurses responsible for vaccine preparation and administration
Study Sites	25 centers in India
Study Sponsor	Bharat Biotech International Limited
Type of report available as of this rapid review	Preprint
Others	
Trial subject disposition - Not vaccinated Withdrawn from vaccination - Discontinued from vaccination - Withdrawal by subject - Discontinuation due to AE - Lost to ff-up Withdrawn from study - Withdrawal by subject - Lost to ff-up - Adverse event Efficacy Populations - Excluded from Dose 1 pop - Excluded from Dose 2 pop - Excluded from 7 days pop - Did not receive Dose 2 - Protocol deviation	Trial subject disposition - Not vaccinated: 45 Withdrawn from vaccination - Discontinued from vaccination: 1334 - Withdrawal by subject: 486 - Discontinuation due to AE: 23 - Lost to ff-up: 361 Withdrawn from study: 408 - Withdrawal by subject: 151 - Lost to ff-up: 232 - Adverse event: 3 Efficacy Populations - Excluded from Dose 1 pop: 45 - Excluded from Dose 2 pop: 1334 - Excluded from 7 days pop: - Did not receive Dose 2: 1334 - Protocol deviation

Appendix 3. Risk of Bias Assessment of Included Studies

STUDY ID	STUDY DESIGN	RANDOMIZATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF INVESTIGATORS	BLINDING OF ASSESSORS	MISSING OUTCOMES/ FOLLOW UP	SELECTIVE REPORTING	OVERALL CONTROL FOR CONFOUNDERS
Ella et al July 2021	RCT	Low	Low	Low	Low	Low	Low	High	Unclear
Singh et al 2021	Prospective cohort	N/A	N/A	N/A	N/A	N/A	Low	Low	High

Appendix 4. Characteristics of Studies on the Real-World Evidence of BBV152

Study ID	Design	Population	Intervention	Comparison	Follow up	Outcomes Reported
Singh et al 2021 N = 515	Prospective Cohort Study	>18 years old, health care workers who received first dose of vaccine, including COVID-19 recovered (>6 weeks before first dose)	Covishield	Covaxin	Day 21 after first dose, Day 21-28 of second dose, Day 83-97 (3 months), and Day 173-187 (6 months) after second dose	• SARS-CoV-2 spike antibody positivity rates after first dose of vaccine • Comparison of SARS-CoV-2 spike antibody between Covishield and Covaxin • Post vaccination (second dose) adverse events) • Post vaccination SARS-CoV-2 infection

Appendix 5. Characteristics and Results of Studies on the Effectiveness of BBV152 against Variants of Concern

Study ID	Population (n)	Variants Tested	Reference Strain	Immunologic Parameter (Test Used)	Extraction time	Result
Sapkal JTM	38	Alpha	hCoV-19/India/2020770 and hCoV-19/India/2020Q111	Neutralizing antibody titers (PRNT50)	Not mentioned	Titers not statistically significant across strains
Kant	*Heterologous group:* 18 participants: 11 male, 7 female; median age of 62 years, *Homologous groups:* 40 individuals each; CS (22 males, median age of 65.5 years), CV (23 females, median age of 56 years)	Alpha, Beta and Delta strains	B.1	Geometric mean titre (GMT)	9 weeks after second vaccine dose	GMTs for CV group against: - B1: 156.6 (95% CI 105.2-233.1) - Alpha: 112.4 (95% CI:76.56-164.9), ***1.39-fold reduction*** - Beta: 52.09 (95% CI 34.9-77.73) ***3.00-fold reduction*** - Delta: 54.37 (95% CI 27.26-108.4) ***2.88-fold reduction*** GMTs for heterologous group against: - B1: 539.54 (95% CI 263.9-1103) - Alpha: 396.1(95% CI 199.1-788) ***1.36-fold reduction*** - Beta: 151 (95% CI 80.2-284.3) ***3.57-fold reduction*** - Delta: 241.2 (95% CI 74.99-775.9) ***2.24-fold reduction*** ***Heterologous titers higher than homologous (3-fold higher)***
Yadav	20 COVID-19 recovered cases	Beta and Delta variants	B.1 (D614G)	Geometric mean titre (GMT)	28 days after 2 doses of Covaxin	GMTs for vaccinees sera against: - Beta: 61.57 (95% CI 36.3 4-104.3) - Delta: 68.97 (95% CI 24.72-192.4) - B1: 187.5 (95% CI 129.3 –271.9) GMT ratio of B.1 to: - Beta: 3.3 (95% CI 2.4-4.5) - Delta: 4.6 (95% CI: 2.2-9.5) ***Fold reduction (computed)*** ***Beta: 3.04-fold*** ***Delta: 2.72-fold*** Significant reduction in neutralization titre for Beta and Delta variants in comparison to B.1 (P value <0.0001)

Appendix 6. Summary of Findings Table of Efficacy of BBV152

Efficacy Outcome (at >14 days after dose2)		Quality Assessment					Summary of Findings			Certainty
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine n/N (%)	Control n/N (%)	Vaccine Efficacy (CI)	
1: Symptomatic COVID-19 infection, seronegative at baseline	1 RCT	Serious Short ff-up	Not assessed	Not serious	Not serious	Serious	24/8471 (0.28)	106/8502 (1.25)	77.8 (65.2-86.4)	+++ Moderate
2: Severe COVID-19 infection, seronegative at baseline	1 RCT	Serious Short ff-up	Not assessed	Not serious	Not serious	Serious	1/8471 (0.01)	15/8505 (0.18)	93.4 (57.1-99.8)	+++ Moderate
3. Asymptomatic COVID-19 infection, seronegative at baseline	1 RCT	Serious Short ff-up	Not assessed	Not serious	serious	Very Serious	13/3248 (0.40)	33/3041 (1.09)	63.6 (29-82.4)	++ Low
4. Any COVID-19 infection, seronegative at base line	1 RCT	Serious Short ff-up	Not assessed	Not serious	Not serious	Serious	19/3248 (0.58%	56/3041 (1.84)	68.8 (46.7-82.5)	+++ Moderate
5: Symptomatic COVID-19 infection, older adults (>=60yo), seronegative at baseline	1 RCT	Serious Short ff-up	Not assessed	Not serious	Serious	Very Serious	5/893 (0.56)	16/965 (1.66)	67.8 (8-90)	++ Low
6. Symptomatic COVID-19 infection, with pre-existing medical condition (at risk for severe infection)	1 RCT	Serious Short ff-up	Not assessed	Not serious	Not serious	Serious	12/2328 (0.52)	37/2518 (1.47)	66.2 (33.8-84)	+++ Moderate
7. Symptomatic COVID-91 infection, children (<18yo)	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
8. Any COVID-19 infection, B.1.1.7/Alpha variant	1 RCT	Serious Missing data Short ff-up	Not assessed	Not serious	Serious (very low event counts)	Very Serious	1/8471 (0.01)	3/8502 (0.04)	—	++ Low
9. Any COVID-19 infection, B.1.151/Beta variant	2 OBS	Very serious Uncontrolled confounders	Not serious	Serious immunologic	Not assessed	Very Serious	(titers)	(titers)	reduced	+ very Low
10. Any COVID-19 infection, B.167.2/Delta lineage	1 OBS	Serious Missing data Short ff-up	Not assessed	Not serious	Not serious	Not serious	13/8471 (0.15)	37/8502 (0.44)	65.2 (33.1-83)	+ Low

Appendix 7. Summary of Findings Table on the Safety of BBV152

COMPARISON : BBV152 vs placebo									
Safety Outcome	**Quality Assessment**					**Summary of Findings**			**Certainty**
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Relative Risk (95%CI)**	
1: Solicited adverse reaction	Not serious	Not serious	Not serious	Serious	Serious	1223/12879 (9.5%)	1136/12874 (8.8%)	1.08 (0.996 to - 1.162)	+++ Moderate
2: Local adverse reaction	Not serious	Not serious	Not serious	Serious	Serious	709/12879 (5.5%)	659/12874 (5.12%)	1.08 (0.97 to - 1.19)	+++ Moderate
3: Any systemic adverse events	Not concern	Not serious	Not serious	Not serious	Not Serious	562/12879 (4.4%)	452/12874 (3.5%)	1.24 (1.1-1.40)	++++ High
4: Serious adverse event	Serious (short ff-up)	Not serious	Not serious	Not serious	Serious	39/12879 (0.30%)	60/12874 (0.47%)	0.64 (0.43-0.97)	+++ Moderate
5: Related serious adverse event (All medically attended adverse events (MAAEs)	Serious (short ff-up)	Not serious	Not serious	Serious	Serious	301/12879 (2.3%)	319/12874 (2.5%)	0.94 (0.81-1.1)	++ Low
6: Withdrawals due to adverse event	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
7: Death	Not serious (short ff-up)	Not serious	Not serious	Serious	Serious	5/12879 (0.04%)	10/12874 (0.08%)	0.5 (0.17-1.46)	+++ Moderate

Appendix 8. Ongoing Trials Registered at the Clinicaltrials.gov Registry on BBV152

NCT Number	Title	Status	Outcome Measures	Age	Phases	Study Designs	Completion Date	Locations	URL
NCT04471519	Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) for COVID-19 in Healthy Volunteers	Active, not recruiting	Phase 1: Occurrence of adverse events and Serious Adverse events|Phase 2: Evaluation of Neutralizing Antibody Titers|Phase 1: Evaluation of Neutralizing Antibody Titers|Phase 2: Occurrence of adverse events and Serious Adverse events	12 Years to 65 Years Â (Child, Adult, Older Adult)	Phase 1|Phase 2	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	30-Jun-21	King George Hospital, Visakhapatnam, Andhra Pradesh, India|All India Institute of Medical Sciences, Patna, Bihar, India|Pt BD SHARMA,PGIMS/UHS, Rohtak, Haryana, India|Jeevan Rekha Hospital, Belgaum, Karnataka, India|Gillukar Multispeciality Hospital, Nagpur, Maharastra, India|All India Institute of Medical Sciences, Delhi, New Delhi, India|Institute of Medical Sciences and SUM Hospital, Bhubaneswar, Orissa, India|SRM Hospital & Research center, Chennai, Tamilnadu, India|Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India|Rana Hospital and Trauma Center, Gorakhpur, Uttar Pradesh, India|Prakhar Hospital, Kanpur, Uttar Pradesh, India|Redkar Hospital and Research Centre, Goa, India	https://ClinicalTrials.gov/show/NCT04471519
NCT04641481	An Efficacy and Safety Clinical Trial of an Investigational COVID-19 Vaccine (BBV152) in Adult Volunteers	Active, not recruiting	First occurrence of Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19.|First occurence of Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 based on the case definition for the secondary efficacy symptomatic endpoint.|Virologically confirmed (RT-PCR positive) severe cases of COVID-19|Virologically confirmed COVID-19 cases of any severity occurring among participants 18 through 59 years of age and â‰¥60 years of age.|Virologically confirmed COVID-19 asymptomatic and symptomatic cases occurring from two weeks after the second vaccination.|Reactogenicity and Safety|The occurrence of enhanced respiratory disease episodes.|Immunogenicity: Lot-to-Lot consistency of three consecutive GMP Lots|Geometric Mean Titer (GMT) of SARS-CoV-2 Specific Neutralizing Antibody (nAb)	18 Years to 99 Years Â (Adult, Older Adult)	Phase 3	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Prevention	Dec-22	Pt BD SHARMA,PGIMS/UHS, Rohtak, Haryana, India	https://ClinicalTrials.gov/show/NCT04641481
NCT04918797	COVAXIN in a Pediatric Cohort	Recruiting	Reactogenicity|Immunogenecity|Immunogenicity	2 Years to 18 Years Â (Child, Adult)	Phase 2|Phase 3	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Prevention	25-Jan-22	Victoria Government Hospital, Visakhapatnam, Andhra Pradesh, India|All India Institute of Medical Sciences, Patna, Bihar, India|Cheluvambha Hospital, Mysore, Karnataka, India|Meditrina Institute of Medical Sciences, Nagpur, Maharashtra, India|Jawahar Lal Nehru Medical college, Ajmer, Rajasthan, India|Pranam Hospitals Hyderabad, Hyderabad, Telangana, India|Prakhar Hospital, Kanpur, Uttar Pradesh, India	https://ClinicalTrials.gov/show/NCT04918797
NCT04834869	COVID-19 Vaccines Safety Tracking (CoVaST)	Recruiting	Local Side Effects|Systemic Side Effects|Unrecognized Side Effects	18 Years and older Â (Adult, Older Adult)		Observational Model: Other|Time Perspective: Prospective	31-Jan-22	American College of Physicians, Philadelphia, Pennsylvania, United States|McMaster University, Hamilton, Ontario, Canada|University of Split, Split, Croatia|Masaryk University, Brno, Czechia|University of Tartu, Tartu, Estonia|Jimma University, Jimma, Ethiopia|Justus-Liebig University Giessen, Giessen, Germany|University of Ghana, Accra, Ghana|Sinaloa's Pediatric Hospital, CuliacÃ¡n, Mexico|Medical University of Silesia, Katowice, Poland|Nursing School of Coimbra, Coimbra, Portugal|Irkutsk Scientific Center of Siberian Branch of Russian Academy of Sciences, Irkutsk, Russian Federation|University of Belgrade, Belgrade, Serbia|University of Ljubljana, Ljubljana, Slovenia	https://ClinicalTrials.gov/show/NCT04834869