Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial

*Raches Ella, Siddarth Reddy, William Blackwelder, Varsha Potdar, Pragya Yadav, Vamshi Sarangi, Vinay K Aileni, Suman Kanungo, Sanjay Rai, Prabhakar Reddy, Savita Verma, Chandramani Singh, Sagar Redkar, Satyajit Mohapatra, Anil Pandey, Pajanivel Ranganadin, Raghavendra Gumashta, Manish Multani, Shameem Mohammad, Parul Bhatt, Laxmi Kumari, Gajanan Sapkal, Nivedita Gupta, Priya Abraham, Samiran Panda, Sai Prasad, Balram Bhargava, Krishna Ella, Krishna Mohan Vadrevu, on behalf of the COVAXIN Study Group**

Summary

Background We report the clinical efficacy against COVID-19 infection of BBV152, a whole virion inactivated SARS-CoV-2 vaccine formulated with a toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG) in Indian adults.

Methods We did a randomised, double-blind, placebo-controlled, multicentre, phase 3 clinical trial in 25 Indian hospitals or medical clinics to evaluate the efficacy, safety, and immunological lot consistency of BBV152. Adults (age ≥18 years) who were healthy or had stable chronic medical conditions (not an immunocompromising condition or requiring treatment with immunosuppressive therapy) were randomised 1:1 with a computer-generated randomisation scheme (stratified for the presence or absence of chronic conditions) to receive two intramuscular doses of vaccine or placebo administered 4 weeks apart. Participants, investigators, study coordinators, study-related personnel, the sponsor, and nurses who administered the vaccines were masked to treatment group allocation; an unmasked contract research organisation and a masked expert adjudication panel assessed outcomes. The primary outcome was the efficacy of the BBV152 vaccine in preventing a first occurrence of laboratory-confirmed (RT-PCR-positive) symptomatic COVID-19 (any severity), occurring at least 14 days after the second dose in the per-protocol population. We also assessed safety and reactogenicity throughout the duration of the study in all participants who had received at least one dose of vaccine or placebo. This report contains interim results (data cutoff May 17, 2021) regarding immunogenicity and safety outcomes (captured on days 0 to 56) and efficacy results with a median of 99 days for the study population. The trial was registered on the Indian Clinical Trials Registry India, CTRI/2020/11/028976, and ClinicalTrials.gov, NCT04641481 (active, not recruiting).

Findings Between Nov 16, 2020, and Jan 7, 2021, we recruited 25 798 participants who were randomly assigned to receive BBV152 or placebo; 24 419 received two doses of BBV152 (n=12 221) or placebo (n=12 198). Efficacy analysis was dependent on having 130 cases of symptomatic COVID-19, which occurred when 16 973 initially seronegative participants had at least 14 days follow-up after the second dose. 24 (0·3%) cases occurred among 8471 vaccine recipients and 106 (1·2%) among 8502 placebo recipients, giving an overall estimated vaccine efficacy of 77·8% (95% CI 65·2–86·4). In the safety population (n=25 753), 5959 adverse events occurred in 3194 participants. BBV152 was well tolerated; the same proportion of participants reported adverse events in the vaccine group (1597 [12·4%] of 12 879) and placebo group (1597 [12·4%] of 12 874), with no clinically significant differences in the distributions of solicited, unsolicited, or serious adverse events between the groups, and no cases of anaphylaxis or vaccine-related deaths.

Interpretation BBV152 was highly efficacious against laboratory-confirmed symptomatic COVID-19 disease in adults. Vaccination was well tolerated with no safety concerns raised in this interim analysis.

Funding Bharat Biotech International and Indian Council of Medical Research.

Published **Online** November 11, 2021 https://doi.org/10.1016/S0140-6736(21)02000-6

See **Online/Comment** https://doi.org/10.1016/S0140-6736(21)02014-6

*All members listed in appendix 1 (pp 2–5)

Bharat Biotech International, Hyderabad, India (R Ella MBBS, S Reddy MSc, V Sarangi BSc, V K Aileni PhD, S Prasad MBA, K Ella PhD, K M Vadrevu PhD); **WB Statistical Consulting, Bethesda, MA, USA** (W Blackwelder PhD); **National Institute of Virology, Indian Council of Medical Research, Pune, India** (V Potdar PhD, P Yadav PhD, G Sapkal PhD, P Abraham PhD); **National Institute of Cholera and Enteric Diseases, Indian Council of Medical Research, Kolkatta, India** (S Kanungo MD); **All India Institute of Medical Sciences, New Delhi, India** (S Rai MD); **Nizams Institute of Medical Sciences, Hyderabad, India** (P Reddy MD); **Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, India** (S Verma MD); **All India Institute of Medical Sciences, Patna, India** (C Singh MD); **Redkar Hospital, Panjim, India** (S Redkar MD); **SRM Hospital and Research Centre, Chennai, India** (S Mohapatra MD); **ESIC Medical College and Hospital, Faridabad, India** (A Pandey MD); **Mahatma Gandhi Medical College and Research Institute, Pondicherry, India** (P Ranganadin MD); **Department of Community Medicine, People's College of Medical Sciences and Research Centre, People's University, Bhopal, India** (R Gumashta MD); **Rahate Surgical Hospital, Nagpur, India** (M Multani MD); **Aligarh Muslim University,**

Introduction

The COVID-19 pandemic, caused by the novel human coronavirus SARS-CoV-2, requires vaccines from multiple manufacturers to address the global demand, as current supplies are insufficient to protect the global population. The widely publicised mRNA-based and viral vector vaccines, although shown to be effective, introduce problems with cold chain supply and vaccine wastage, making them difficult to adopt for many countries.

Bharat Biotech International has developed BBV152, a COVID-19 vaccine based on the whole virion SARS-CoV-2 vaccine strain NIV-2020-770 (spike variant Asp614Gly) inactivated with β-propiolactone. Preclinical studies in

Aligarh, India (S Mohammad MD)**; GMERS Medical College and Civil Hospital, Ahmedabad, India** (P Bhatt MD)**; Government Fever Hospital, Guntur, India** (L Kumari MD)**; Indian Council of Medical Research, New Delhi, India** (N Gupta MD, S Panda MD, B Bhargava MD)

Correspondence to: Dr Krishna Mohan Vadrevu, Bharat Biotech International, Hyderabad 500 078, India **kmohan@bharatbiotech.com**

See **Online** for appendix 1

For the **WHO COVID-19 dashboard** see https://covid19.who.int/

Research in context

Evidence before this study

Several effective vaccines against SARS-CoV-2 have been developed in response to the global COVID-19 pandemic via different methodologies, mainly directed at the SARS-CoV-2 spike protein. The literature describes many different techniques to elicit antibodies against the spike protein including mRNA coding for the protein, protein subunit vaccines, and whole-virus inactivated vaccines.

On Sept 25, 2021, we searched PubMed for "SARS-CoV-2 vaccine" AND "clinical trial" AND "efficacy" with no date or language restrictions, and identified 205 reports. With newly emerging variants of concern (VOCs) including the delta (B.1.617.2) variant, there are questions about the efficacy of the first used vaccines against these VOCs. Bharat Biotech International have developed a β-propiolactone-inactivated whole-virus vaccine, BBV152, formulated with a toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG), which has been shown to be safe, immunogenic, and capable of stimulating a T-cell memory response in phase 1 and 2 studies. Efficacy of this vaccine against all severities of symptomatic COVID-19 disease, asymptomatic COVID-19 infection, and disease due to the delta variant has not been studied previously.

Added value of this study

This study showed the clinical efficacy of BBV152 against symptomatic COVID-19 disease. In this randomised, placebo-controlled, phase 3 trial, 24 419 adult participants with no serological evidence of previous exposure to SARS-CoV-2 received two doses of BBV152 vaccine or placebo, 4 weeks apart. Efficacy against any severity of COVID-19 with onset 14 days after the second vaccination was 77·8% (95% CI 65·2–86·4), and efficacy against severe COVID-19 was 93·4% (57·1–99·8). Efficacy against asymptomatic COVID-19 was 63·6% (29·0–82·4). Our preliminary analysis found an efficacy of 65·2% (95% CI 33·1–83·0) against the delta variant, but further investigations are necessary to confirm clinical efficacy against this variant and others. Safety monitoring and reactogenicity assessments of BBV152 did not raise concerns about the vaccine.

Implications of all the available evidence

This study shows that the BBV152 vaccine is generally effective against COVID-19, preventing symptomatic disease and decreasing severity and the need for hospitalisation.

rodents and non-human primates have shown appropriate tolerability, immune responses, and protective efficacy.[1–3] We previously reported interim findings from phase 1 and 2 controlled, randomised, double-blind trials on the safety, reactogenicity, and immunogenicity of different formulations, which resulted in the selection of a formulation containing a 6 µg vaccine dose with a toll-like receptor 7/8 agonist molecule (imidazoquinoline; IMDG) adsorbed to alum (Algel-IMDG) for further clinical development.[4,5] In use, BBV152 is stored between 2°C and 8°C, which could ease immunisation cold chain requirements. Our primary objective was to assess the efficacy of BBV152 in preventing RT-PCR-confirmed symptomatic COVID-19 in a case-driven manner, with secondary subgroup analyses according to disease severity, age, health status, and symptom status. In this Article, we report interim results from a phase 3 case-driven efficacy study, including a subset analysis of efficacy against newly identified SARS-CoV-2 variants of concern (VOCs) and variants of interest (VOIs). We also present results on the safety and immunogenicity of the selected BBV152 formulation, including the regulatory requirement of comparing immune responses to three consecutive manufacturing lots measured 1 month after the second dose.

See **Online** for appendix 2

Methods

Study design and participants

We assessed the efficacy, safety, and immunological lot consistency of two intramuscular 6 µg Algel-IMDG doses of BBV152 vaccine (Bharat Biotech International, Hyderabad, India) in a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial done at 25 hospitals or medical clinics in India (appendix 1 pp 2–5). The trial was approved by the National Regulatory Authority of India and the respective ethics committees of each study centre, and was conducted in compliance with the International Conference for Harmonisation Good Clinical Practice Guideline.

Participants were adult volunteers aged 18 years or older who were healthy or had stable chronic medical conditions. A stable condition was defined as a disease not requiring significant change in therapy or hospitalisation or that did not worsen during the 3 months before enrolment. Volunteers were screened for eligibility on the basis of their health status, including medical history, vital signs, and physical examination results. Key exclusion criteria included any diagnosis with an immunocompromising condition, or treatment with immunosuppressive therapy. Detailed inclusion and exclusion criteria are provided in the protocol (appendix 2 pp 44–45). A minimum of 20% of the entire sample size was to be comprised of participants at high risk of severe consequences of COVID-19 infection, defined as either being aged 60 years or older, having a coexisting comorbidity (cardiovascular, diabetes, or any other chronic stable condition), or having a body-mass index of at least 35 kg/m². Additionally, a maximum of 5% of all enrolled participants were selected from members of the health-care community. Eligible participants provided signed and dated informed consent forms at enrolment.

Randomisation and masking

Unmasked statisticians (Cytespace Research, Bengaluru, India, and Octalsoft, Gujarat, India) designed the randomisation plan and the interactive web response system (IWRS) system to generate treatment allocation for the study, stratified for the presence or absence of chronic conditions. The master randomisation list, containing the randomisation number and intended treatment allocation, and the vaccination kit code, was sent to the IWRS and kits were despatched to the sites according to the IWRS by an unmasked statistician from a contract research organisation (IQVIA, India) tasked with labelling of vaccine vials and the generation of the master randomisation code. Randomisation was 1:1 to receive two doses of BBV152 or placebo 4 weeks apart, except for the 600 participants enrolled for the immunogenicity analysis for whom randomisation was 3:1 in a sequence to ensure equal distribution to the three lots of BBV152. Randomisation was also done, with stratification in mind for the presence or absence of chronic conditions, to ensure equal distribution of at-risk participants who were distributed 1:1 to the vaccine or placebo groups. Participants, investigators, study coordinators, study-related personnel, and the sponsor (Bharat Biotech International) were masked to the treatment group allocation, and masked study nurses at each site were responsible for vaccine preparation and administration. Vaccine and placebo had identical appearance, colour, and viscosity. Masked laboratory assessments were done at Bharat Biotech International, and masked datasheets were sent to IQVIA for decoding and analysis. The unmasked randomisation list was not shared with the study sponsor. Endpoints were judged by an independent adjudication committee masked to treatment allocation. This committee assessed the case files for each suspected case of COVID-19 and confirmed each case on the basis of standard definitions and severity of illness. The committee also assessed whether any deaths were COVID-related.

Procedures

BBV152 is a whole virion β-propiolactone-inactivated SARS-CoV-2 vaccine. The vaccine strain NIV-2020-770, sequenced by the Indian Council of Medical Research National Institute of Virology (ICMR-NIV; Pune, India), contains the Asp614Gly mutation in the spike protein.[6] Each 0·5 mL dose contains 6 μg of virus antigen formulated with Algel-IMDG. Placebo vials contained the Algel formulation alone without IMDG or inactivated virus antigen. Vaccine and placebo were supplied and stored in single-use glass vials at 2–8°C, with no on-site dose preparation necessary.

Full eligibility screening was done at the first vaccination visit on day 0 (visit 1). At visit 1, participants were evaluated with SARS-CoV-2 real-time RT-PCR (ICMR-NIV 2019 nCoV Assay Kit V 3.1) and a serology test (ICMR-NIV Anti-SARS CoV-2 Human IgG ELISA COVID KAVACH—MERILISA; both from ICMR-NIV, Pune, India), before the injection (appendix 1 pp 6–7). Regardless of the outcome of these tests, participants were randomly allocated with the IWRS in a 1:1 ratio to receive two intramuscular doses of vaccine or placebo on day 0 and day 28 (visit 2), and received the first dose. After the first dose, participants who were subsequently found to have a positive RT-PCR test were excluded from receiving the second dose. All women had a urine pregnancy test at each vaccination visit and those who tested positive excluded. The ICMR-NIV RT-PCR test has been validated by the WHO external quality assurance assessment scheme. The ICMR-NIV ELISA test was validated by ICMR-NIV.

Participants were monitored for 2 h after vaccination for any acute reactions. Prophylactic medication (ibuprofen or acetaminophen) was allowed but no instruction was given to specifically administer prescribed prophylactics in participants either before or after vaccination. Participants were instructed to record local and systemic reactions daily for 7 days after each vaccination (days 0 to 7 and days 28 to 35) using a paper-based memory aid which solicited local and systemic adverse events. Solicited local adverse events included pain and swelling at the injection site, and systemic adverse events included fever, fatigue or malaise, myalgia, arthralgia, headache, nausea or vomiting, and chills. The memory aid contained fields for symptom onset, severity, time to resolution, and concomitant medications and was collected during the subsequent study visit or telephone contact. Routine telephone calls were scheduled daily for the first 7 days after each vaccination. Participants reported all unsolicited adverse events and serious adverse events throughout the study. Adverse events were graded according to severity (mild, moderate, or severe) and by relationship (related or unrelated) to the investigational vaccine by the principal investigator at each site as detailed in the protocol (appendix 2 pp 70–71) Adverse events of special interest (anaphylaxis, generalised convulsions, or any vaccine-associated enhanced respiratory disease) were assessed by the investigators and an independent data and safety monitoring board.

Study sites were classified into three categories. At category 1 sites (n=17 sites; appendix 1 pp 2–5) where, in addition to administering the vaccine or placebo, a series of post-vaccination follow-up telephone calls (once every 2 weeks) were used to detect suspected symptomatic COVID-19 and those who met symptomatic criteria had a clinical assessment (appendix 2 pp 20–24), and a nasopharyngeal swab was taken for PCR confirmation. At category 2 sites (n=5; appendix 1 pp 2–5), in addition to symptomatic follow-up, a series of post-vaccination nasopharyngeal swabs (1 swab per visit) were collected on-site for detection of asymptomatic COVID-19 infection at monthly intervals up to month 7. At category 3 sites (n=3; appendix 1 pp 2–5), in addition to follow-up for symptomatic and asymptomatic COVID-19 infection,

blood samples were collected on-site for immunological assessments. The three category 3 sites were selected to be geographically spread and the first 200 participants at each of these sites were automatically selected to be in the immunogenicity cohort. The complete assessment schedules for all three site categories are shown in the protocol (appendix 2 pp 27–29). We had planned to include a fourth category of sites in Brazil, but recruitment proved too difficult and was discontinued without analysis. Unscheduled illness visits were encouraged for participants up to month 12 (day 360 plus or minus 14 days; ie, the end of study follow-up for participants). All participants were instructed to contact the team on an as-needed basis.

Outcomes

The primary outcome was the efficacy of the BBV152 vaccine in preventing a first occurrence of symptomatic COVID-19 (any severity) with onset at least 14 days after the second dose, assessed centrally by IQVIA. Symptomatic COVID-19 was defined by the presentation of at least two symptoms that included fever (temperature ≥38°C), chills, new cough, myalgia, headache, sore throat, diarrhoea, nausea, or congestion; or at least one event of new-onset anosmia or ageusia, a respiratory sign or symptom (shortness of breath or difficulty breathing, oxygen saturation <94% or requirement for supplemental oxygen, or radiographic evidence of pneumonia), evidence of shock, or intensive care admission or death (appendix 2 pp 23–24). These criteria had to be met in addition to at least one SARS-CoV-2-positive nasopharyngeal swab tested by PCR. For PCR confirmation of COVID-19 we used the ICMR-NIV real-time RT-PCR assay. The kit has one SARS-CoV-2 screening gene (*E* gene) and two confirmatory genes (*ORF1b* and *RdRp*) along with the housekeeping gene β-actin to provide a robust detection system for conclusive results for suspected cases of SARS-CoV-2. The kit can detect all currently circulating variants of SARS-CoV-2 and showed 100% specificity and 98·8–100% sensitivity on evaluation in the ten laboratories used for our analysis.

For the **WHO page on tracking SARS-CoV-2 variants** see https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

COVID-19 cases were followed up daily by telephone to assess symptom severity until symptoms resolved or the patient required hospitalisation for severe COVID-19 (recorded as a severe adverse event). A secondary outcome was vaccine efficacy against severe COVID-19. We defined severe COVID-19 according to the US Food and Drug Administration (FDA) definition, which requires RT-PCR-confirmed COVID-19 with one of the following additional features: clinical signs at rest that are indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurological dysfunction; admission to an intensive care unit; or death.[7] In RT-PCR-positive participants who consented, an additional nasopharyngeal swab for genotyping and a blood sample for evaluating correlates of protection were collected. Further secondary efficacy outcomes included efficacy in subgroups defined by age (18–59 years and ≥60 years), efficacy against VOCs, and efficacy against asymptomatic infections (and combined symptomatic and asymptomatic infections). Asymptomatic infection was defined as RT-PCR-confirmed SARS-CoV-2 infection detected from the monthly swabs with none of the prespecified COVID-19 symptoms, reported after receipt of two doses of vaccine or placebo (≥14 days since second dose). Post-hoc efficacy analysis was conducted in subgroups according to health risk for severe disease (presence or absence of a coexisting chronic medical condition).

Our immunological secondary outcome was the equivalence of immune responses to three consecutive vaccine lots, to meet the regulatory requirement of consistency of manufacture for commercial lots. We nested this immunogenicity analysis in our efficacy study as advised by the FDA.[7] Equivalence was based on geometric titres (GMTs) of SARS-CoV-2-specific neutralising antibodies evaluated with a wild-type virus microneutralisation titre 50% (MNT_{50}) assay (appendix 1 p 10). Additionally, consistency of immune responses against three SARS-CoV-2 epitopes (the S1 protein and the receptor-binding domain [RBD] of the spike protein, and the nucleocapsid protein [N protein]) were measured as IgG responses by ELISA (appendix 1 p 8) on day 0 and day 56. The RBD and N protein analyses were performed post hoc. All sera were analysed in a blinded manner at Bharat Biotech International (Hyderabad, India) and submitted to IQVIA for data analysis and preparation of the report. Post-hoc immune response calculations were conducted in subgroups according to age, gender, and serostatus (seronegative *vs* seropositive) at baseline. Safety secondary outcomes in this report are the proportions of participants with solicited local and systemic reactogenicity within 7 days after the first and second dose, and with unsolicited adverse events recorded within 28 days after each dose.

As the emergence of VOCs and VOIs occurred during the conduct of our trial, additional informed consent was obtained to collect nasopharyngeal swabs from symptomatic participants with RT-PCR-confirmed COVID-19 to identify the strain responsible. All sequences were generated by the NIV using a quantitative next-generation sequencing approach (appendix 1 p 9).[8,9] Negative controls from participants with RT-PCR-confirmed negativity who provided informed consent were checked to ensure that the negative tests had no evidence of amplification and that expected RNA quantification was consistent with cycle threshold (Ct) values provided by the testing laboratories. Post-hoc assessments of symptomatic COVID-19 infections between vaccine and placebo recipients were conducted to determine viral loads for variants on the basis of Ct values from RT-PCR.

Statistical analysis

The study was designed to obtain a two-sided 95% CI for vaccine efficacy with a lower bound of 30%. Based on a true efficacy of 60% and 85% power, the case-driven trial was planned to accrue 130 cases. Assuming 1% incidence of PCR-confirmed symptomatic COVID-19 disease among placebo recipients during follow-up beginning 14 days after the second dose, the number of participants required to accrue 130 cases was approximately 18 572. To allow for a 20% baseline seropositivity rate or PCR-confirmed COVID-19 and 10% loss to follow-up, we planned to enrol 25 800 participants. Thus the maximum cap on randomisation was 25 800 participants. For the nested immunogenicity cohort, for an SD of 0·4 for serum neutralising antibody titre, 150 participants were required in each lot. The power to obtain a two-sided 95% CI that falls within the interval 0·5–2·0, was approximately 98·1%, for a true GMT ratio of 1·3. For a GMT ratio of less than 1·3 for each of the three pairwise comparisons, the power to show lot consistency (ie, that the two-sided 95% CI falls within the interval 0·5–2·0 for each pairwise comparison) was greater than 95%. Thus we enrolled 600 participants (450 receiving vaccine, 150 receiving placebo). Sample size estimation was performed with PASS software (version 13).

The primary outcome was assessed in the per-protocol population, composed of participants who were SARS-CoV-2-negative by serology at baseline (day 0), had no major protocol deviations (as assessed by the sponsor), and followed up for at least 14 days after the second dose. Estimation of vaccine efficacy was based on person-time incidence rates: efficacy=1–(nv/Fv)/(np/Fp)=1–R, where R=(nv/Fv)/(np/Fp); nv and np are the numbers of participants who develop PCR-confirmed symptomatic COVID-19 among BBV152 vaccine and placebo recipients, respectively, and Fv and Fp are the corresponding total lengths of follow-up in years in the two groups, with follow-up in years defined as follow-up in days divided by 365·25. We also define the parameter P, the proportion of participants with COVID-19 who were in the vaccine group. Then a two-sided CI around the estimated vaccine efficacy is obtained by converting an exact CI for the probability parameter P, with the observed Fp/Fv, to a CI for vaccine efficacy. Interim analyses were planned at 43 and 87 primary endpoint cases, with use of an O'Brien-like Lan-DeMets alpha spending function.[10] The accumulation of COVID-19 cases in the per-protocol set with onset from day 42 (14 days after the second dose) are presented in a Kaplan-Meier plot for the BBV152 and placebo groups.

Safety endpoints were assessed in all participants who received at least one dose of vaccine or placebo, reported as number and percentage of participants. Immunological endpoints in the per-protocol population are expressed as GMTs with 95% CIs calculated from 95% CIs for means of $\log_{10}$(titre), which used t-distributions. The criterion for consistency (equivalence) of the immune response to BBV152 across three consecutive manufacturing batches was that two-sided 95% CIs for the ratio of GMTs for all pairs of lots be entirely contained within the interval 0·5–2·0. These limits have frequently been used for the related concept of non-inferiority in vaccine trials.[11]

Exact binomial calculations were used for the 95% CI estimation for vaccine efficacy. Wilson's score test was used to test differences in proportions. This report contains interim results (data cutoff May 17, 2021) regarding immunogenicity outcomes (captured on days 0 to 56; day 56 being 1 month after the second dose) and safety outcomes (median follow-up 146 days; captured for at least 84 days for all participants, 2 months after the second dose as per FDA safety regulations), and efficacy results with a median of 99 days for the study population (starting 14 days after the second dose). Certain prespecified subgroup and immunogenicity analyses are not included in this report but will be presented in future analyses when a larger dataset is available; a full report of safety analyses will also be provided when the study is completed. Descriptive and inferential statistics were performed with SAS (version 9.4). The independent data and safety monitoring board periodically reviewed unmasked efficacy and safety data. The trial was registered on Clinical Trials Registry India, CTRI/2020/11/028976, and on ClinicalTrials.gov, NCT04641481, and is active for safety monitoring (closed to recruitment).

For **PASS 13** see https://www.ncss.com/download/pass/updates/pass13/

Role of the funding source

Bharat Biotech International and ICMR were responsible for designing the protocol. The funders of the study had no role in data collection or data analysis. Bharat Biotech International provided technical guidance on deriving methodologies for data analysis. Representatives of Bharat Biotech International interpreted the data (RE and KMV) and prepared this manuscript (RE). IQVIA was responsible for overall trial conduct and data analysis.

Results

Between Nov 16, 2020, and Jan 7, 2021, we screened 26 028 volunteers, of whom 25 798 were enrolled and randomly assigned, and 25 753 participants across 25 sites received the first dose of BBV152 vaccine (n=12 879) or placebo (n=12 874) and comprised the safety population (figure 1; appendix 1 p 12). After enrolment, a first dose of vaccine or placebo was administered to 16 477 participants at category 1 sites, 5313 participants at category 2 sites, and 4008 participants at category 3 sites. At the data cutoff of May 17, 2021, 23 803 (92·4%) of 25 753 participants had a median of 146 days of safety data available after the first dose. The dropout rate by day 84 was 6·7% (12 028 of 12 899 remaining in the BBV152 group and 12 046 of 12 899 remaining in the placebo group), affecting both groups equally, with the main reason being withdrawal of consent due to unwillingness of participants to attend during the second wave of COVID-19 infections in India.

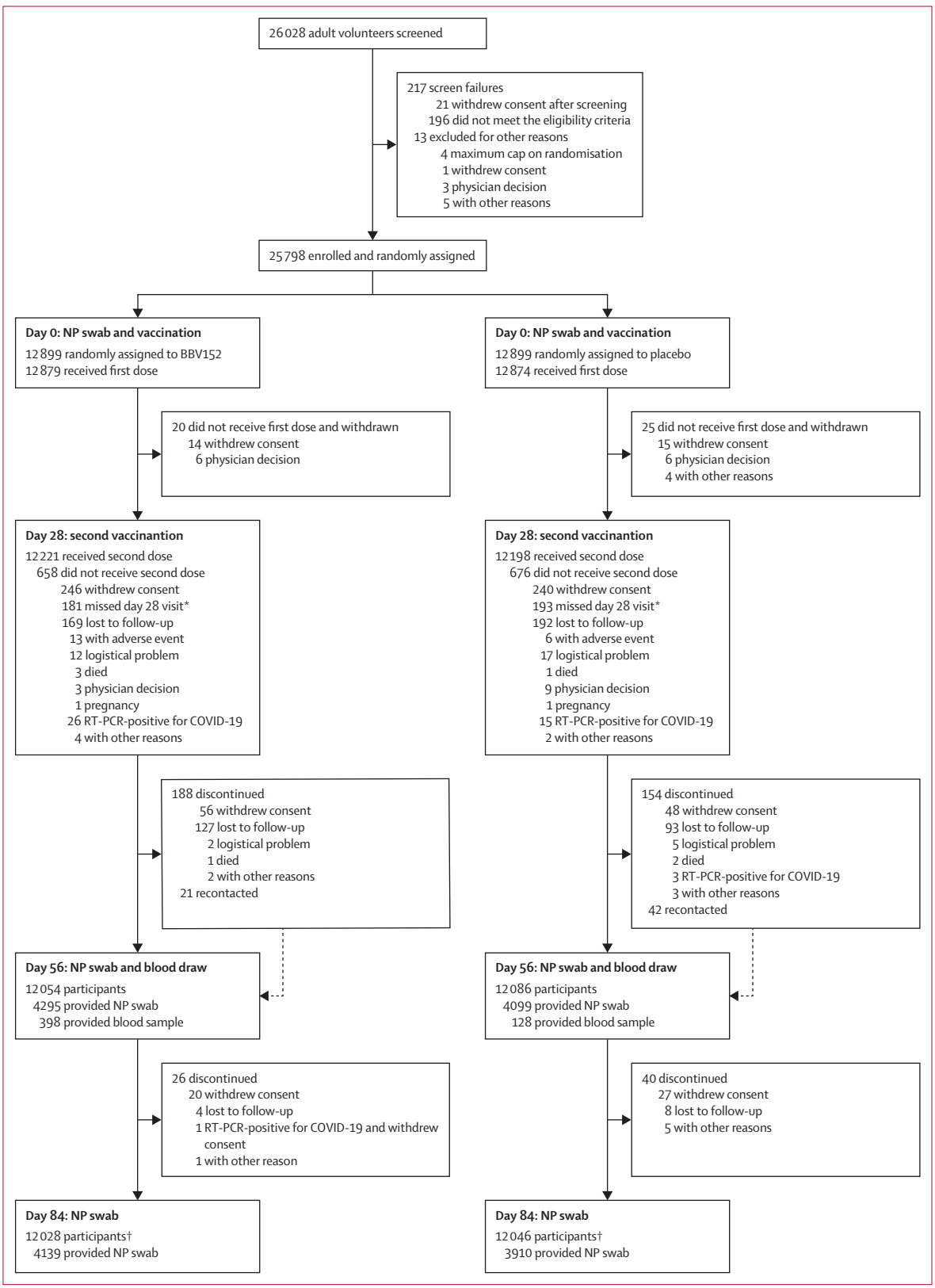

Figure 1: **Trial profile**
NP=nasopharyngeal. *Safety follow-up ongoing. †119 participants in the BBV152 group and 152 in the placebo group did not attend the day 84 visit but were not lost to follow-up or discontinued.

Among the 25753 participants in the safety population, 5724 (22·2%) had at least one coexisting chronic condition. Mean age was 40·1 years (SD 13·8), and 2761 (10·7%) participants were aged 60 years or older (mean 66·9 years [5·8]). A large proportion of participants were seropositive at baseline (3932 [30·5%] of 12879 in the BBV152 group and 3886 [30·2%] of 12874 in the placebo group) and were thus excluded from the per-protocol analysis but contributed to the safety dataset. All baseline characteristics were similar between the vaccine and placebo groups (table 1), and baseline SARS-CoV-2 seropositivity and exposure to SARS-CoV-2 infection were similar across the different categories of site when accounting for differences in sample size (appendix 1 p 11).

24419 participants received two doses of BBV152 (n=12221) or placebo (n=12198; figure 1). Among these participants, 16973 were included in the per-protocol population (appendix 1 p 12). 41 RT-PCR-confirmed COVID-19 cases occurred between receiving the first and second doses and, by definition of the primary outcome (first occurrence of symptomatic COVID-19 with onset at least 14 days after the second dose), these participants were not included in the per-protocol analyses. The planned efficacy analysis occurred after the accrual of 130 symptomatic COVID-19 cases during follow-up beginning 2 weeks after the second vaccination (figure 2). A total of 684 suspected COVID-19 cases were identified at least 14 days after the second dose, of which 139 (20·3%) were confirmed by RT-PCR. Of the confirmed cases, nine did not meet the case definition, being either seropositive for SARS-CoV-2 at baseline or only having one symptom, and thus 130 cases were included in the efficacy analysis. 24 (0·3%) cases occurred among 8471 participants in the vaccine group and 106 (1·2%) among 8502 participants in the placebo group, resulting in an estimated vaccine efficacy of 77·8% (95% CI 65·2–86·4; table 2). 16 cases met the definition for severe symptomatic COVID-19: one in the vaccine group and 15 in the placebo group, resulting in a vaccine efficacy of 93·4% (57·1–99·8). Based on monthly nasopharyngeal swabs (collected at a median of 31 days), efficacy against asymptomatic COVID-19 infections was 63·6% (29·0–82·4). In 1858 older participants (≥60 years) in the analysis, the split of symptomatic cases between the vaccine and placebo groups was five (0·6%) of 893 participants and 16 (1·7%) of 965, respectively, giving an efficacy of 66·2% (33·8–84·0). Efficacy in the 15115 participants who were younger than 60 years was 79·4% (66·0–88·2; table 2).

At day 56, in the immunogenicity groups who received vaccine lots 1, 2, and 3, the GMTs of SARS-CoV-2 neutralising antibodies (expressed as MNT_{50}) were 130·3 (95% CI 105·8–160·4), 121·2 (97·6–150·5), and 125·4 (101·3–155·1), respectively. GMT for the placebo group was 13·7 (10·7–17·4; table 3). GMT ratios between all three pairs of lots were similar: for lots 1 and 2, the ratio was 1·08 (95% CI 0·80–1·45), for lots 1 and 3, the ratio was 1·04 (0·77–1·40), and for lots 2 and 3, the ratio was 0·97 (0·71–1·31). All the 95% CIs for the GMT ratios were contained within the interval 0·5–2·0 (appendix 1 p 13), meeting the predefined criterion for a consistent immune response across lots.

	BBV152 (N=12 879)	Placebo (N=12 874)
Age, years	40·1 (13·8)	40·1 (14·1)
Range	18–92	19–97
Sex		
Female	4214 (32·7%)	4254 (33·0%)
Male	8665 (67·3%)	8620 (66·9%)
BMI, kg/m²	24·3 (4·4)	24·3 (4·3)
Pre-existing medical conditions		
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 kg/m²)	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%)

Data are mean (SD) or n (%) unless otherwise stated. BMI=body-mass index. *At the screening and first vaccination visit (day 0, visit 1) participants were evaluated for exposure to SARS-CoV-2 with both anti-SARS-CoV-2 IgG by ELISA and RT-PCR. Regardless of the outcome of these tests, participants were randomly assigned and received the first dose of vaccine or placebo.

Table 1: **Demographic characteristics of participants in the safety population (N=25 753)**

We found no marked differences in GMTs for neutralising antibodies at day 56 when assessed according to age or gender (appendix 1 p 14). The GMT was significantly higher, based on 95% CIs, in vaccine recipients who were seropositive for SARS-CoV-2 IgG at baseline (194·3 [95% CI 134·4–280·9], n=48] than in those who were seronegative (118·0 [104·0–134·0], n=338).

At day 56, IgG titres for the assayed epitopes (S1 protein, RBD, and N protein) were detected after two doses. For all three lots combined, the GMTs at day 56 (expressed as arbitrary ELISA units per mL) were 9742 (95% CI 8949–10606) for S1 protein, 4124 (3731–4557) for RBD, and 4161 (3736–4633) for N protein (table 3). The placebo group did not show any meaningful change from baseline in titres during the course of the study for any of the immune targets.

In the analysis of confirmed symptomatic COVID-19 cases among the per-protocol population, a total of 79 variants were reported from 16973 samples, 18 in the vaccine group and 61 in the placebo group (table 4). Among 50 cases confirmed to be positive for the delta (B.1.617.2) variant, 13 were in the vaccine group and 37 were in the placebo group, resulting in a vaccine efficacy of 65·2%

(95% CI 33·1–83·0). In symptomatic delta (B.1.617.2) variant infections, based on Ct values, the viral load in the vaccine group was significantly lower than in the placebo group (mean ratio of BBV152 to placebo 1·42 [1·28–1·57]; appendix 1 p 21). Efficacy against the kappa (B.1.617.1) variant was 90·1% (30·4–99·8). No cases of severe variant-related COVID-19 were reported in the vaccine recipients, but four severe cases were reported in the placebo recipients infected with the alpha (B.1.1.7), kappa (B.1.617.1), delta (B.1.617.2), and unclassified variants, respectively (table 4).

Regarding safety outcomes (median follow-up 146 days after the first dose), there were 15 deaths during the study, none of which were considered by the investigators to be related to vaccine or placebo; six deaths were reported to be related to COVID-19. Five deaths occurred in BBV152 recipients, attributed to cerebellar haemorrhage, haemorrhagic stroke, ovarian cancer with metastases, sudden cardiac death, and COVID-19 (n=1 each). Ten deaths occurred in placebo recipients, attributed to alcohol overdose, myocardial infarction, cardiac arrest with underlying hypertension (n=1 each), COVID-19 (n=5), and so far undetermined (n=2). No anaphylactic events were reported.

The vaccine had a good reactogenicity profile with similar proportions of participants reporting solicited, unsolicited, and serious adverse events and adverse events of special interest in the vaccine and placebo groups (appendix 1 p 15). Serious adverse events occurred in 99 participants; 39 (0·3%) who had received BBV152 and 60 (0·5%) who had received placebo (appendix 1 pp 17–19). One serious adverse event possibly related to study treatment occurred in the BBV152 group; a case of immune thrombocytopenic purpura 39 days after the second dose in a vaccine recipient who was SARS-CoV-2-seropositive at baseline. The event resolved in 4 days. All other serious adverse events were deemed unrelated to vaccine or placebo. Long-term safety monitoring is ongoing and will continue for 1 year after administration of the first dose of BBV152.

Adverse events are reported for all 25 753 participants who received a first dose (appendix 1 p 15). 5959 adverse events occurred in 3194 participants. The proportion of participants reporting any adverse events was the same after vaccine (1597 [12·4%] of 12 879 participants) or placebo (1597 [12·4%] of 12 874). The proportion of participants reporting any adverse events within 7 days after vaccination was lower after the second dose (1116 [4·3%] of 25 753) than after the first dose (1511 [5·9%]) of either vaccine or placebo, and slightly higher in the BBV152 group than in the placebo group (809 [6·3%] *vs* 702 [5·5%] after first dose, 568 [4·4%] *vs* 548 [4·3%] after second dose; appendix 1 p 15). Among the local or systemic solicited adverse events, only local injection pain was reported in more than 1% of participants after the first or second dose of vaccine or placebo (appendix 1 p 16). Similar proportions of vaccine recipients (392 [3·0%]) and

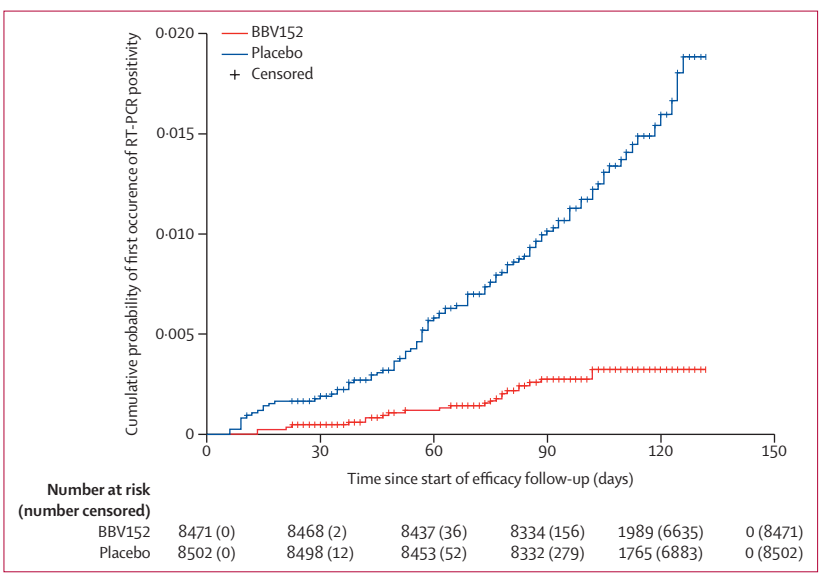

Figure 2: **Kaplan Meier plot of first occurrence of RT-PCR-confirmed symptomatic cases of COVID-19**
Data are for the per-protocol set from day 42 (day 0 in the figure), 14 days after the second vaccination.

	Total cases	BBV152	Placebo	Vaccine efficacy, % (95% CI)*
Symptomatic COVID-19	130/16 973 (0·8%)	24/8471 (0·3%)	106/8502 (1·2%)	77·8% (65·2–86·4)
Severe symptomatic COVID-19	16/16 973 (0·1%)	1/8471 (<0·1%)	15/8502 (0·2%)	93·4% (57·1–99·8)
Symptomatic COVID-19 in participants aged 18–59 years	109/15 115 (0·7%)	19/7578 (0·3%)	90/7537 (1·2%)	79·4% (66·0–88·2)
Symptomatic COVID-19 in participants aged ≥60 years	21/1858 (1·1%)	5/893 (0·6%)	16/965 (1·7%)	67·8% (8·0–90·0)
Symptomatic COVID-19 in participants with a pre-existing chronic medical condition	49/4846 (1·0%)	12/2328 (0·5%)	37/2518 (1·5%)	66·2% (33·8–84·0)
Asymptomatic COVID-19	46/6289 (0·7%)	13/3248 (0·4%)	33/3041 (1·1%)	63·6% (29·0–82·4)
Symptomatic and asymptomatic COVID-19	75/6289 (1·2%)	19/3248 (0·6%)	56/3041 (1·8%)	68·8% (46·7–82·5)

Data are n/N (%) unless otherwise stated. *95·006% CI used for primary analysis of symptomatic COVID-19 to adjust for interim analyses, 95% CI otherwise. Primary efficacy was based on the 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 RT-PCR-confirmed SARS-CoV-2 infection before the start of efficacy follow-up. Symptomatic COVID-19 cases were defined as occurring in participants who had at least two symptoms that included fever (temperature ≥38°C), chills, new cough, myalgia, headache, sore throat, diarrhoea, nausea, or congestion; or at least one event of new-onset anosmia or ageusia, a respiratory sign or symptom (shortness of breath or difficulty breathing, oxygen saturation <94% or requirement for supplemental oxygen, or radiographic evidence of pneumonia), evidence of shock, or intensive care admission or death; and at least one nasopharyngeal swab that was PCR-positive for SARS-CoV-2.

Table 2: **BBV152 vaccine efficacy against SARS-CoV-2 after at least 14 days after the second dose in the per-protocol population (N=16 973)**

placebo recipients (358 [2·8%]) reported local pain after the first dose, with proportions decreasing after the second dose (233 [1·8%] and 208 [1·6%], respectively). Other local adverse events were reported by fewer than 0·3% of participants in either group after the first or second dose. Solicited systemic adverse events were reported less frequently, in 331 (2·6%) vaccine recipients and 247 (1·9%) placebo recipients after the first dose, and 231 (1·8%) and 205 (1·6%) recipients after the second dose. The most frequent solicited systemic adverse event overall was headache, followed by pyrexia (fever), fatigue, and myalgia, but in lower than 1% of participants in either group. The BBV152 and placebo groups had similar proportions affected by mild (693 [5·4%] *vs* 646 [5·0%]), moderate (16 [0·1%] *vs* 13 [0·1%]), and severe (0 in both groups) local solicited adverse events, and similar proportions affected by mild (534 [4·1%] *vs* 419 [3·3%]), moderate (27 [0·2%] *vs* 33 [0·3%]), and severe (1 [<0·1%] *vs* 0) systemic solicited adverse events (appendix 1 p 16). Unsolicited adverse events were reported by 489 (3·8%) vaccine recipients and 609 (4·7%) placebo recipients (appendix 1 p 15). No clinically meaningful differences were observed in the reported rates of solicited or unsolicited adverse events between the vaccine and placebo groups.

Discussion

We report findings from a phase 3 efficacy, safety, and immunogenicity clinical trial of BBV152, a whole virion inactivated SARS-CoV-2 vaccine. In the final per-protocol analysis, measured 14 days after the second of two doses of BBV152, we estimated a vaccine efficacy of 77·8% (95% CI 65·2–86·4) against symptomatic COVID-19 disease and, importantly, based on the limited data available, a higher efficacy against severe COVID-19 of 93·4% (57·1–99·8). Thus, cases of severe disease, which require hospitalisation and have threatened to overwhelm health-care facilities, could be markedly decreased in fully vaccinated populations. Additionally, although the study was not powered to definitively assess efficacy in subgroups categorised by age or the presence of pre-existing comorbid conditions, efficacy against symptomatic COVID-19 was high in these groups (>66%) with the lower limits of the respective 95% CIs being higher than 30% in all cases except for the older age group (≥60 years). The number of older participants was lower than anticipated, representing less than 11% of the study cohort. Nonetheless, 1858 older participants were included in the efficacy analysis, and the resulting efficacy rate had a lower confidence bound greater than zero; this result can thus be considered meaningful according to FDA guidance.[7]

This phase 3 study was done during a period that included the second wave of COVID-19 infections in India, with a peak of more than 400 000 new cases per day (appendix 1 p 20), when BBV152 was assessed against all circulating variants. The study confirms our previous observations on the safety and immunogenicity profiles of BBV152 in phase 1 and 2 trials.[4,5] No safety concerns were raised, no anaphylactic events after BBV152 administration were reported, and all adverse events (solicited, unsolicited, and serious adverse events) were well balanced between the BBV152 and placebo groups. After the first or second dose, the combined incidence of local and systemic adverse events in this study is better than rates for other SARS-CoV-2 vaccine platform candidates,[12,13] and similar to rates for other inactivated SARS-CoV-2 vaccine candidates.[14–16] However, such a comparison of adverse events needs to be interpreted with caution given that other vaccine studies enrolled different populations and

	BBV152: lot 1	BBV152: lot 2	BBV152: lot 3	BBV152: all lots	Placebo
SARS-CoV-2 neutralising antibody					
Day 0: participants	132	129	136	397	125
Day 0: GMT (95% CI)	9·9 (8·3–11·9)	8·6 (7·5–9·9)	7·9 (7·0–8·9)	8·8 (8·0–9·6)	8·9 (7·7–10·4)
Day 56: participants	128	125	133	386	119
Day 56: GMT (95% CI)	130·3 (105·8–160·4)	121·2 (97·6–150·5)	125·4 (101·3–155·1)	125·6 (111·2–141·8)	13·7 (10·7–170·4)
S1 protein-binding IgG					
Day 56: participants	129	124	134	387	121
Day 56: GMT (95% CI)	9760 (8483–11 228)	10 404 (8873–12 198)	9152 (7912–10 586)	9742 (8949–10 606)	1528 (1323–1765)
RBD-binding IgG					
Day 56: participants	129	124	134	387	121
Day 56: GMT (95% CI)	4266 (3584–5079)	4423 (3669–5333)	3740 (3180–4399)	4124 (3731–4557)	1443 (1261–1651)
N protein-binding IgG					
Day 56: participants	129	124	134	387	121
Day 56: GMT (95% CI)	4551 (3800–5450)	4183 (3423–5111)	3798 (3165–4558)	4161 (3736–4633)	1485 (1275–1730)

Data are shown for neutralising antibody response expressed as MNT_{50} at day 0 (baseline) and day 56 (4 weeks after the second vaccination). Day 56 IgG antibody titres are expressed as arbitrary ELISA units per mL, all baseline titres being at the cutoff for the assay (reciprocal of 1:500 dilution). GMT=geometric titre. MNT_{50}=microneutralisation titre 50%. N protein=nucleocapsid protein. RBD=receptor-binding domain. S1=spike protein S1 subunit.

Table 3: **SARS-CoV-2 neutralising antibody titres (MNT_{50} assay) and binding antibody responses (ELISA; S1 protein, RBD, and N protein IgGs)**

	Total number (N=16 973)*	BBV152 (N=8471)	Placebo (N=8502)	Vaccine efficacy, % (95% CI)
All variants	79 (0·5%)	18 (0·2%)	61 (0·7%)	70·8% (50·0 to 83·8)
B.1.617.2 (delta)	50 (0·3%)	13 (0·2%)	37 (0·4%)	65·2% (33·1 to 83·0)
B.1.617.1 (kappa)	11 (0·1%)	1 (<0·1%)	10 (0·1%)	90·1% (30·4 to 99·8)
B.1.1.7 (alpha)	4 (<0·1%)	1 (<0·1%)	3 (<0·1%)	..
Other†	14 (0·1%)	3 (<0·1%)	11 (0·1%)	73·0% (−2·2 to 95·2)
All variants (severe COVID-19)	4 (<0·1%)	0	4 (<0·1%)‡	..

Data are n (%) unless otherwise stated. Data include per-protocol population only. In those participants who met the definition for symptomatic COVID-19 and were PCR-positive an additional nasopharyngeal swab for genotyping was collected. Nasopharyngeal swabs with cycle threshold value greater than 30 were not genotyped. We were unable to retrieve the complete genome from six swab samples that were sequenced (all in the placebo group), and these samples weren't included in the analysis. *79 of 130 positive cases in the per-protocol set were sequenced. †Other pangolin variants detected were Asp614Gly (n=7), B.1.36 (n=2), B.1.1.419, B.1.153, B.1.351, B.1.618, and A.1 (all n=1 each). ‡Alpha, kappa, delta, and unclassified variants (n=1 each).

Table 4: **Efficacy against variants of interest and variants of concern**

employed varying approaches to measure adverse events, and head to head comparisons are necessary to conclude on this point. When measured by neutralising antibodies or by ELISA, IgG responses against three SARS-CoV-2 epitopes (S1 protein and RBD of the spike protein, and the N protein), antibody titres were similar across the three consecutive manufacturing lots.

The surge in SARS-CoV-2 variant strains has raised concerns regarding the efficacy of vaccines against the new VOCs. Some COVID-19 vaccines, notably CoronaVac and ChAdOx1, have been reported to have diminished efficacy against the gamma (P.1) and beta (B.1.351) variants first isolated in Brazil and South Africa.[12,13] The ChAdOx1 vaccine has shown equivalent efficacy against the alpha (B.1.1.7) variant, which is widely circulating.[17] Effectiveness after two doses of the mRNA-based vaccine BNT162b2 is 93·4% (95% CI 90·4–95·5) against alpha (B.1.1.7) and 87·9% (78·2–93·2) against delta (B.1.617.2).[18] ChAdOx1 effectiveness after two doses is 66·1% (54·0–75·0) against alpha (B.1.1.7) and 59·8% (28·9–77·3) against delta (B.1.617.2).[17] In previous reports, BBV152-induced antibodies showed no statistically significant decrease in neutralisation activity against alpha (B.1.1.7), but showed 2–3-times reductions in neutralisation activity of the B.1.1.28, beta (B.1.351), kappa (B.1.617.1), gamma (P.1), and delta (B.1.617.2) variants.[19–22] In our preliminary analysis, we found an efficacy of 65·2% (95% CI 33·1–83·0) against the delta (B.1.617.2) variant, but further investigations are necessary and will be made to confirm clinical efficacy against this variant and others throughout the remainder of the study.

Our efficacy and safety findings are corroborative of previous results for an alum-alone adjuvanted inactivated SARS-CoV-2 vaccine (Sinopharm, Beijing, China), which showed 78% (95% CI 65–86) efficacy.[16] However, that study reported few severe symptomatic cases, did not report efficacy against VOCs, and post-hoc assessment of asymptomatic efficacy was not done by routine nucleic acid testing. No licensed SARS-CoV-2 vaccine has reported efficacy against asymptomatic infection in a randomised controlled trial on the basis of nucleic acid testing, although the mRNA vaccine BNT162b2 has been associated with decreased asymptomatic SARS-CoV-2 infections in health-care workers.[23] Several other vaccine studies have employed surrogate markers to assess asymptomatic efficacy; the study on BNT162b2 periodically collected serum from trial participants and assessed for binding antibody against the SARS-CoV-2 N protein.[23] In this study, 8721 participants at category 2 sites made monthly clinical visits for routine medical checkups and collection of nasopharyngeal swabs for PCR confirmation of asymptomatic COVID-19 (collected at a median of 31 days). In the per-protocol set, we tested 3248 participants in the BBV152 group and 3041 in the placebo group for asymptomatic COVID-19. As per the cutoff date, up to 2 months after the second dose, 13 and 33 positive cases had been confirmed by PCR in the vaccine and placebo groups, respectively, giving an efficacy of 63·6% (95% CI 29·0 to 82·4). A study with the ChAdOx1 vaccine found no efficacy (3·8% [–72·4 to 46·3]) against asymptomatic infections, although direct comparisons cannot be made as a surrogate serological marker was used.[12] Our findings indicate that BBV152 might provide moderate upper airway protection via reduction of viral loads, and corroborate well with preclinical protective efficacy studies in hamsters and non-human primates, which reported lower and upper airway protection against SARS-CoV-2 infection.[2,3]

This study has several limitations. Due to the low number of cases reported between the first and second doses, we cannot calculate vaccine efficacy after a single dose. This report contains a median safety follow-up of 146 days from the first dose for all participants, and long-term safety follow-up of BBV152 is required and currently underway. For operational reasons the analysis of efficacy against asymptomatic infection was restricted to 8721 participants, and some cases would have been missed in the rest of the study cohort. However, this would be expected to have affected both vaccine and placebo groups equally. Nonetheless this study is, to our knowledge, the largest to evaluate efficacy against asymptomatic infection and the number studied was sufficient to demonstrate efficacy (as indicated by the lower bound of the CI [29·0] being much higher than 0).[7] The data presented on efficacy against variants other than delta should be considered preliminary as the numbers reported are small. Additional efforts to assess the clinical efficacy of BBV152 against VOCs in this study and others are being planned. The potential establishment of a correlate of protection is not feasible for the cutoff time in this report. The study population also lacked ethnic and racial diversity, highlighting the importance of evaluating the efficacy of BBV152 in other populations.

The study was designed to vaccinate and follow participants for 1 year after the second dose; however, given the nature of the pandemic in India and the emergency use authorisation of BBV152, after meeting the predefined efficacy success criteria, the data and safety monitoring board and sponsor decided to unmask participants in the placebo group who were eligible to receive an approved COVID-19 vaccine. Unmasking in such cohorts was planned only after the accrual of the prespecified 130 cases, in a phased manner: first health-care professionals, then individuals aged 45 years or older, followed by those aged younger than 45 years. Our sample estimations accounted for 20% seropositivity. Despite the low dropout rate, as we observed baseline seropositivity rates of 30% and due to the unmasking of health-care professionals and elderly individuals (who are eligible for COVID-19 vaccination), the protocol was amended to expand the sample size to 30 800, with the intention of enrolling 5000 participants in Brazil. However, the exacerbating conditions in Brazil mean recruitment for a placebo-controlled trial is now too

difficult. As the data is from an Indian cohort only it reflects the racial and ethnic diversity of the Indian population, so should not be applied to different populations. We had intended to cover low population diversity with the proposed recruitment in Brazil. Furthermore, some groups including pregnant women, people living with HIV, or people with severe comorbidities were specifically excluded and further investigations will be required to support the use of the vaccine in such groups.

However, this study does have several strengths. We enrolled participants of ages 18–98 years and found no major differences in immune responses across the broad age groups of younger (<60 years) and older (≥60 years) participants. Participants considered to be at-risk of acquiring COVID-19 were prioritised, so a total of 2761 participants were aged 60 years or older, and 5724 reported at least one pre-existing chronic medical condition across ages. To ensure generalisability, this study was conducted with participants from diverse geographical locations, enrolling 25 798 participants across 25 hospitals.

The most common solicited adverse event was pain at the injection site, followed by headache, fever, and fatigue. No severe or life-threatening (grade 4 and 5; appendix 2 pp 65–67) solicited adverse events were reported. Although the study was not powered to find safety differences and the sample size was based on the power to determine efficacy, no meaningful safety differences were observed between the groups.

The positive safety, immunogenicity, and efficacy results presented here can support regulatory submissions for emergency use authorisation. With the inclusion of vaccine vial monitors (category type 7), storage at 2–8°C, and a 28-day open-vial policy (limiting open-vial vaccine wastage by an estimated 10–25% on the basis of other multidose vaccines), the established efficacy of BBV152 against symptomatic infection could be crucial in further mitigating the COVID-19 pandemic. The asymptomatic efficacy highlighted in our study had wide confidence intervals, necessitating further data. However, the result still has public health significance in terms of reducing transmission.

Contributors

All authors met the criteria for authorship set by the International Committee of Medical Journal Editors. RE contributed to manuscript preparation. KMV, SPr, KE, WB, NG, SPa, PA, and BB reviewed the manuscript. KMV interpreted data. RE and KMV were responsible for overall project coordination. SidR, VS, and VKA led clinical operations and helped to design the protocol. WB was involved with designing the study and statistical analysis plan. VP, PY, and GS led the virological confirmation and genomic sequencing efforts. The contract research organisation (IQVIA) was responsible for analysing the data and generating a data report. All principal investigators (SK, SanR, PRe, SV, CS, SagR, SM, AP, PRa, RG, MM, SM, PB, and LK) were involved in the scientific review of this paper. RE, KMV, PY, GS, VKA, and VS accessed and verified the masked data in the study, and confirmed its accuracy and completeness. All authors had full access to all data in the study. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

This work was funded by Bharat Biotech International and co-funded by the Indian Council of Medical Research. RE, KMV, SPr, SRe, VKA and VS are employees of Bharat Biotech International, with no stock options or incentives. KE is the chairman and managing director of Bharat Biotech International and owns equity in the company. WB is an independent statistical development consultant. VP, PY, GS, PA, NG, BB, SK, and SPa are employees of the Indian Council of Medical Research. All other authors declare no competing interests.

Data sharing

The study protocol is provided in appendix 2 (pp 1–91). Individual de-identified participant data will be made available when the trial is complete on direct request to the corresponding author with an appropriate research proposal. If such a proposal is approved data will be shared via a secure online platform.

Acknowledgments

We are sincerely thankful to the volunteers, investigators, study coordinators, and health-care workers involved in this study. We express our gratitude to the teams at IQVIA, Cytespace, and Octalsoft who contributed to the trial. Dr Shashi Kanth Muni, Dr Yuvraj Jogdand, Dr Ashwini Maratha, Dr Sapan Kumar Behera, Dr Amarnath Reddy Kowkuntla, Dr Jagadish Kumar, Dr Bhargav Reddy, Sandhya Rani, Aparna Bathula, Nagaraju Pillutla, and Sunil Kumar Kantheti of Bharat Biotech International participated in protocol design and clinical trial monitoring. We thank the members of the data and safety monitoring board and adjudication committee for their continued support and guidance of this ongoing clinical study. The vaccine candidate could not have been developed without the efforts of the manufacturing, quality control, and marketing teams of Bharat Biotech International. We are grateful to Keith Veitch (Keithveitch communications, Amsterdam, Netherlands) for editorial assistance with the manuscript.

References

1 Ganneru B, Jogdand H, Daram VK, et al. Th1 skewed immune response of whole virion inactivated SARS CoV 2 vaccine and its safety evaluation. *iScience* 2021; **24:** 102298.

2 Yadav PD, Ella R, Kumar S, et al. Immunogenicity and protective efficacy of inactivated SARS-CoV-2 vaccine candidate, BBV152 in rhesus macaques. *Nat Commun* 2021; **12:** 1386.

3 Mohandas S, Yadav PD, Shete-Aich A, et al. Immunogenicity and protective efficacy of BBV152, whole virion inactivated SARS-CoV-2 vaccine candidates in the Syrian hamster model. *iScience* 2021; **24:** 102054.

4 Ella R, Vadrevu KM, Jogdand H, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. *Lancet Infect Dis* 2021; **21:** 637–46.

5 Ella R, Reddy S, Jogdand H, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. *Lancet Infect Dis* 2021; **21:** 950–61.

6 Sarkale P, Patil S, Yadav PD, et al. First isolation of SARS-CoV-2 from clinical samples in India. *Indian J Med Res* 2020; **151:** 244–50.

7 US Food and Drug Administration Centre for Biologics Evaluation and Research. Development and licensure of vaccines to prevent COVID-19: guidance for industry. June, 2020. https://www.fda.gov/media/139638/download (accessed June 19, 2021).

8 Choudhary ML, Vipat V, Jadhav S, et al. Development of in vitro transcribed RNA as positive control for laboratory diagnosis of SARS-CoV-2 in India. *Indian J Med Res* 2020; **151:** 251–54.

9 Yadav PD, Potdar VA, Choudhary ML, et al. Full-genome sequences of the first two SARS-CoV-2 viruses from India. *Indian J Med Res* 2020; **151:** 200–09.

10 DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. *Stat Med* 1994; **13:** 1341–52.

11 Donken R, de Melker HE, Rots NY, Berbers G, Knol MJ. Comparing vaccines: a systematic review of the use of the non-inferiority margin in vaccine trials. *Vaccine* 2015; **33:** 1426–32.

12 Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; **397:** 99–111.

13 Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B.1.351 variant. *N Engl J Med* 2021; **384:** 1885–98.

14 Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis* 2021; **21:** 181–92.

15 Xia S, Duan K, Zhang Y, et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials. *JAMA* 2020; **324:** 951–60.

16 Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. *JAMA* 2021; **326:** 35–45.

17 Bernal JL, Andrews M, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med* 2021; **385:** 585–94.

18 Emary KRW, Golubchik T, Aley PK, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. *Lancet* 2021; **397:** 1351–62.

19 Sapkal GN, Yadav PD, Ella R, et al. Inactivated COVID-19 vaccine BBV152/COVAXIN effectively neutralizes recently emerged B.1.1.7 variant of SARS-CoV-2. *J Trav Med* 2021; published online March 27. https://doi.org/10.1093/jtm/taab051.

20 Sapkal G, Yadav PD, Ella R, 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. *J Trav Med* 2021; published online May 17. https://doi.org/10.1093/jtm/taab077.

21 Yadav PD, Sapkal GN, Ella R, et al. Neutralization against B.1.351 and B.1.617.2 with sera of COVID-19 recovered cases and vaccinees of BBV152. *J Trav Med* 2021; published online July 6. https://doi.org/10.1093/jtm/taab104.

22 Yadav PD, Sapkal GN, Abraham P, et al. Neutralization of variant under investigation B.1.617 with sera of BBV152 vaccinees. *Clin Infect Dis* 2021; published online May 7. https://doi.org/10.1093/cid/ciab411.

23 Tang L, Hijano DR, Gaur AH, et al. Asymptomatic and symptomatic SARS-CoV-2 infections after BNT162b2 vaccination in a routinely screened workforce. *JAMA* 2021; **325:** 2500–02.