

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

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30 **NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.**
31

32 **ABSTRACT:**

33 ***Background:***

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

37 ***Methods:***

38 We did a double-blind, randomised, multicentre, phase 3 clinical trial in 25 Indian hospitals
39 to evaluate the efficacy, safety, and immunological lot consistency of BBV152. Healthy
40 adults (age 18–98 years) randomised 1:1 using a computer-generated randomisation scheme
41 received two intramuscular doses of vaccine or placebo administered four weeks apart. The
42 primary outcome was laboratory-confirmed symptomatic COVID-19, occurring at least 14
43 days after the second dose. Secondary outcomes were efficacy in sub-groups for age (18–<
44 60 years and \geq 60 years) and in participants with pre-existing stable medical conditions. We
45 also evaluated safety, reactogenicity, and consistency of immune responses for three
46 consecutive manufacturing lots.

47 ***Findings:***

48 Between November 16, 2020 and January 7, 2021 we recruited 25,798 participants who were
49 randomised to BBV152 or placebo groups; 24,419 received two doses of BBV152 (n =
50 12,221) or placebo (n = 12,198). In a case-driven analysis, 130 cases of symptomatic
51 COVID-19 were reported in 16,973 (0.77%) participants with follow-up at least two weeks
52 after the second vaccination; 24 occurred in the vaccine group and 106 in placebo recipients
53 giving an overall vaccine efficacy of 77.8% (95% CI: 65.2–86.4). Sixteen cases, one
54 vaccinee and 15 placebo recipients, met the severe symptomatic COVID-19 case definition
55 giving a vaccine efficacy of 93.4% (57.1–99.8). Efficacy against asymptomatic COVID-19
56 was 63.6% (29.0–82.4). BBV152 conferred 65.2% (95% CI: 33.1–83.0) protection against

57 the SARS-CoV-2 Variant of Concern, B.1.617.2 (Delta). BBV152 was well tolerated with no
58 clinically or statistically significant differences in the distributions of solicited, unsolicited, or
59 serious adverse events between vaccine and placebo groups. No cases of anaphylaxis or
60 vaccine-related deaths were reported.

61 ***Interpretation:***

62 BBV152 was immunogenic and highly efficacious against symptomatic and asymptomatic
63 COVID-19 variant associated disease, particularly against severe disease in adults.
64 Vaccination was well tolerated with an overall incidence of adverse events observed over a
65 median of 146 days that was lower than that observed with other COVID-19 vaccines.

66 ***Funding:***

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69 [Clinicaltrials.gov](https://clinicaltrials.gov): NCT04641481

70 INTRODUCTION

71 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel human
72 coronavirus, has spread globally causing the COVID-19 pandemic [1]. Vaccines from
73 multiple manufacturers are needed to address the global demand for SARS-CoV-2 vaccines
74 as there is currently insufficient supply. Furthermore, the widely publicised mRNA-based and
75 viral vector vaccines that have been shown to be effective themselves introduce cold chain
76 hurdles and vaccine wastage making them difficult to adopt for many countries.

77 Bharat Biotech has developed BBV152, a COVID-19 vaccine based on the whole-virion
78 SARS-CoV-2 vaccine strain NIV-2020-770 inactivated with β -propiolactone. Preclinical
79 studies in rodents and nonhuman primates (NHP) have demonstrated appropriate tolerability,
80 immune responses and protective efficacy [2–4]. We previously reported interim findings
81 from phase 1 and 2 controlled, randomised, double-blind trials on the safety, reactogenicity
82 and immunogenicity of different formulations, which resulted in the selection of a
83 formulation containing a 6 μ g dose formulated with a Toll-like receptor 7/8 agonist molecule
84 adsorbed to alum (Algel-IMDG) for further clinical development [5,6]. In use, BBV152 is
85 stored between 2°C and 8°C, which will ease immunisation cold chain requirements. Here,
86 we report findings from a phase 3 case-driven efficacy study including a sub-set analysis of
87 efficacy against newly identified variants of SARS-CoV-2. We also present a nested
88 controlled, randomised, double-blind trial on the safety and immunogenicity of the selected
89 BBV152 formulation, including comparisons of immune responses to three consecutive
90 manufacturing lots measured at day 56, one month after the second dose.

91

92 **METHODS**

93 *Study Design and Participants*

94 We assessed the efficacy, safety and immunogenicity of two intramuscular 6 µg Algel-IMDG
95 doses of BBV152 in a randomised, blinded, placebo-controlled, multi-centre study done in 25
96 centres in India. The trial was approved by the National Regulatory Authority (India) and the
97 respective Ethics Committees of each study centre and was conducted in compliance with all
98 International Conference for Harmonization (ICH) Good Clinical Practice guidelines. The
99 trial was registered on clinicaltrials.gov: NCT04641481.

100 Participants were adult volunteers 18 years of age or older who were healthy or had stable
101 chronic medical conditions. Volunteers were screened for eligibility based on their health
102 status, including their medical history, vital signs, and physical examination results. Eligible
103 participants provided signed and dated informed consent forms at enrolment. Key exclusion
104 criteria included any diagnosis with an immunocompromising condition, or treatment with
105 immunosuppressive therapy. Detailed inclusion and exclusion criteria can be found in the
106 Protocol (*Supplementary appendix 2*). A minimum of 20% of the entire sample size was to be
107 comprised of “at-risk participants” defined as being either over 60 years of age, having a
108 coexisting comorbidity (cardio-vascular, diabetes, or any other chronic stable condition), or
109 having a BMI ≥ 35 kg/m². A maximum of 5% of the total enrolled participants were selected
110 from members of the healthcare community.

111 The primary study objective was to assess the efficacy of the study vaccine in preventing
112 PCR-confirmed symptomatic COVID-19 in a case-driven manner, together with sub-group
113 analyses of asymptomatic efficacy and symptomatic efficacy according to age (18–59 and \geq
114 60 years of age), and any chronic stable, medical condition. Major secondary objectives were
115 assessments of the safety and immunogenicity of BBV152 in sub-groups of participants.

116 ***Randomisation and masking***

117 Unblinded statisticians (Cytespace Research and Octalsoft) were involved in designing the
118 randomisation plan and the interactive web response system (IWRS) system for the study.
119 The randomisation plan, stratified for the presence or absence of chronic conditions, was used
120 to generate treatment allocation. The master randomisation list, containing the randomisation
121 number and intended treatment allocation, as well as the kit code, was sent to the IWRS and
122 kits were despatched to the sites according to the IWRS by an unblinded statistician from the
123 CRO tasked with labelling of vaccine vials and the generation of the master randomisation
124 code. Participants were assigned a computer-generated randomisation code and each vial was
125 labelled with a unique code that ensured appropriate masking. The IWRS system assigned the
126 same treatment group for the second visit. Participants, investigators, study coordinators,
127 study-related personnel, and the sponsor were masked to the treatment group allocation, and
128 masked study nurses at each site were responsible for vaccine preparation and administration.

129 ***Procedures***

130 BBV152 (Bharat Biotech, Hyderabad, India) is a whole-virion β -propiolactone-inactivated
131 SARS-CoV-2 vaccine. The vaccine strain NIV-2020-770 contains the D614G mutation,
132 which is characterised by an aspartic acid to glycine shift at amino acid position 614 of the
133 spike protein [7]. Each 0.5 mL dose contains 6 μ g of virus antigen formulated with Algel-
134 IMDG, an imidazoquinoline class molecule that is a Toll-like receptor (TLR) 7/8 agonist
135 (IMDG) adsorbed to Algel. Placebo vials contained the Algel formulation alone without
136 IMDG or inactivated virus antigen. Vaccine and placebo were supplied and stored in a single-
137 use glass vials at 2°C to 8°C, with no on-site dose preparation necessary. The appearance,
138 colour, and viscosity were identical for vaccine and placebo.

139 At the screening/vaccination visit (visit 1), participants were evaluated with both SARS-
140 CoV-2 reverse-transcriptase–polymerase-chain-reaction (PCR) (ICMR-NIV 2019 nCOV
141 Assay Kit V 3.1) and serology tests (Merilisa, ICMR-NIV Anti-SARS CoV-2 Human IgG
142 ELISA COVID KAVACH), before each injection (*Supplementary materials, pages 5–6*).
143 Regardless of the outcome of these tests, participants were randomly allocated using the
144 IWRS in a 1:1 ratio to receive two doses of vaccine or placebo on days 0 and 28. Participants
145 who were subsequently found to have a positive PCR test were excluded from receiving the
146 second dose. All females had a urine pregnancy test.

147 Participants were monitored for 2 hours after vaccination for any acute reactions. No
148 prophylactic medication (ibuprofen/acetaminophen) was prescribed either before or after
149 vaccination. Participants were instructed to record local and systemic reactions daily for
150 seven days after each vaccination (days 0 to 7 and days 28 to 35) using a paper-based
151 memory aid which solicited local and systemic adverse events. Solicited local adverse events
152 included pain at the injection site and swelling, and systemic adverse events included fever,
153 fatigue/malaise, myalgia, body aches, headache, nausea/vomiting, anorexia, chills,
154 generalised rash, and diarrhoea. The memory aid contained fields for symptom onset,
155 severity, time to resolution, and concomitant medications and was collected during the
156 subsequent visit to the site. Routine telephone calls were scheduled following the first seven
157 days after each vaccination. Participants reported all unsolicited adverse events and serious
158 adverse events throughout the study. Adverse events were graded according to severity (mild,
159 moderate, or severe) and by relationship (related or unrelated) to the investigational vaccine,
160 as detailed in the protocol.

161 Study sites were classified into three categories: Category 1: in addition to administering the
162 vaccine or placebo, a series of post-dose follow-up telephone calls (every two weeks) were
163 scheduled to detect suspected symptomatic COVID-19 (n = 16,477) and those who met

164 symptomatic criteria had a clinical assessment (*Protocol, Supplementary appendix 2*), and a
165 nasopharyngeal swab (NP) was taken for PCR confirmation. Category 2: in addition to
166 symptomatic follow-up, a series of post-dose 2 NP swabs were collected on-site for detection
167 of asymptomatic COVID-19 infection at monthly intervals (n = 8,721); Category 3: in
168 addition to follow-up for symptomatic and asymptomatic COVID-19 infection, blood
169 samples were collected for immunological assessments (n = 600). Unscheduled illness visits
170 were encouraged for participants till day 360 (\pm 14 days). All participants were instructed to
171 contact the team on an as-needed basis.

172 ***Outcomes***

173 The primary outcome was the efficacy of the BBV152 vaccine in preventing a first
174 occurrence of symptomatic COVID-19 (any severity) with onset at least 14 days after the
175 second dose in the per-protocol population composed of participants who were SARS-CoV-2
176 negative by PCR and serology at baseline, had no major protocol deviations, and followed-up
177 for at least two weeks after the second dose. End points were judged by an independent
178 adjudication committee masked to treatment allocation. COVID-19 cases were defined as
179 participants with at least two of the following symptoms: fever (temperature \geq 38°C), chills,
180 myalgia, headache, sore throat, or new olfactory or taste disorder, or had at least one
181 respiratory sign or symptom (including cough, shortness of breath, or clinical or radiographic
182 evidence of pneumonia) and at least one SARS-CoV-2 PCR-positive nasopharyngeal swab.
183 COVID-19 cases were followed daily to assess symptom severity until symptoms resolved.
184 In PCR-positive participants who consented, an additional NP swab for genotyping and a
185 blood sample for evaluating correlates of protection were collected. Secondary efficacy
186 outcomes included efficacy in subgroups defined by age (18–59 years and \geq 60 years),
187 gender, and health risk for severe disease (presence or absence of a coexisting chronic
188 medical condition), efficacy against variants of concern, and efficacy against asymptomatic

189 infections occurring after receipt of two doses of vaccine/placebo periodically at a month's
190 interval in 8,721 participants, among whom 6,289 participants were SARS-CoV-2 negative at
191 baseline and included in the per protocol analysis.

192 The immunological secondary outcome was evaluation of consistency of immune responses
193 from three consecutive manufacturing lots. This was based on geometric titres (GMTs)
194 evaluated using a wild-type virus microneutralisation assay (MNT₅₀) (*Supplementary*
195 *materials, page 8*). Immune responses against three SARS-CoV-2 epitopes, the S1 protein
196 and the receptor binding domain (RBD) of the spike protein, and the nucleocapsid antigen
197 (N-antigen) were measured as IgG responses by ELISA (*Supplementary materials, page 9*).
198 All sera were analysed in a blinded manner at Bharat Biotech (Hyderabad, India) and
199 submitted to the CRO for data analysis and preparation of the report. Safety secondary
200 outcomes were the proportions of participants with solicited local and systemic reactogenicity
201 within seven days after vaccination, and with unsolicited adverse events recorded within 28
202 days after vaccination.

203 ***Statistical Analysis***

204 The study was designed to obtain a two-sided 95% CI for vaccine efficacy with lower bound
205 $\geq 30\%$. Based on a true efficacy of 60% and power of 85%, the case-driven trial was planned
206 to accrue 130 cases. Assuming 1% incidence of PCR-confirmed symptomatic COVID-19
207 disease among placebo recipients during follow-up beginning 14 days after the second dose,
208 the number of participants required to accrue 130 cases was approximately 18,572. To allow
209 for a 20% baseline seropositivity rate or PCR-confirmed COVID-19 and 10% loss to follow-
210 up, we planned to enrol 25,800 participants. Sample size estimation was performed using
211 PASS 13 software (NCSS, Kaysville, Utah, USA).

212 Estimation of vaccine efficacy was based on person-time incidence rates: $VE = 1 - (nv/Fv) /$
213 $(np/Fp) = 1 - R$, where $R = (nv/Fv) / (np/Fp)$; nv and np are the numbers of participants who
214 develop PCR-confirmed symptomatic COVID-19 among BBV152 vaccine and placebo
215 recipients, respectively, and Fv and Fp are the corresponding total lengths of follow-up in
216 years in the two groups, with follow-up in years defined as follow-up in days divided by
217 365.25. We also define the parameter P , the proportion of participants with COVID-19 who
218 were in the vaccine group. Then a two-sided confidence interval (CI) around the estimated
219 VE is obtained by converting an exact CI for the probability parameter P , using the observed
220 Fp/Fv , to a CI for VE. Interim analyses were planned at 43 and 87 primary endpoint cases,
221 using an O'Brien-like Lan-DeMets alpha spending function [8].

222 Safety endpoints are reported as number and % of participants. Immunological endpoints are
223 expressed as GMTs with 95% confidence intervals (CIs) calculated from 95% CIs for means
224 of \log_{10} (titre), which used t-distributions. The criterion for consistency (equivalence)
225 (equivalence) of the immune response to BBV152 across three consecutive manufacturing
226 batches was that two-sided 95% CIs for the ratio of GMTs for all pairs of lots be entirely
227 contained within the interval [0.5, 2.0], limits which have frequently been used for the related
228 concept of non-inferiority in vaccine trials [9].

229 For continuous variables (less than 20 observations), medians and IQRs are reported. Exact
230 binomial calculations were used for the CI estimation of proportions. Wilson's score test was
231 used to test differences in proportions. A result with two-sided $P \leq 0.05$ or one-sided $P \leq$
232 0.025 , as appropriate, was considered statistically significant. This report contains results
233 regarding immunogenicity and safety outcomes (captured on days 0 to 56) and efficacy
234 results with a median of 99 days (two weeks after a second dose). Certain prespecified
235 subgroup analyses are not included in this report but will be presented in future analyses

236 when a larger dataset is available. Descriptive and inferential statistics were performed using
237 SAS 9.4.

238 *Role of the Funding Source*

239 Bharat Biotech and the Indian Council of Medical Research (ICMR) were responsible for the
240 funding the study, designing the protocol, and writing this manuscript. The funder of the
241 study had no role in data collection or data analysis. However, the funder provided technical
242 guidance on deriving methodologies for data analysis. A CRO (IQVIA) was responsible for
243 overall conduct and data analysis. Masked laboratory assessments were done at Bharat
244 Biotech, and masked datasheets were sent to the CRO for decoding and analysis. The
245 unmasked randomisation list was not shared with the study sponsor. An independent data and
246 safety monitoring board (DSMB) periodically reviewed unblinded efficacy and unblinded
247 safety data.

248 **RESULTS**

249 Between November 16, 2020 and Jan 7, 2021, we screened 26,028 volunteers and recruited
250 and vaccinated 25,798 participants across 25 sites (**Figure 1**). At the data cut-off date of May
251 17, 2021, a total of 23,803 (92.3%) participants had a median of 146 days of safety data
252 available after the first dose. Among these participants, 7058 (27.5%) had at least one
253 coexisting condition. The mean age was 40.1 years, and 10.7% of participants were older
254 than 60 years of age. A large proportion of participants were seropositive at baseline (30%)
255 and were thus excluded from the per-protocol analysis but contributed to the safety dataset.
256 All baseline characteristics were similar between vaccine and placebo groups (**Table 1**).

257 *Efficacy*

258 Among the 16,973 participants in the per protocol analysis population (*Supplementary table*
259 *2, page 10*), the planned efficacy analysis occurred after the accrual of 130 symptomatic

260 COVID-19 cases which started to present soon after the beginning of the observation period
261 (**Figure 2**). There were 24 (0.28%) cases among 8471 participants in the vaccine arm and
262 106 (1.25%) cases among 8502 participants in the placebo group, resulting in estimated
263 vaccine efficacy of 77.8% (95% CI: 65.2–86.4). There were sixteen cases who met the
264 severe symptomatic COVID-19 cases definition, all but one of whom were in the placebo
265 group, resulting in a vaccine efficacy of 93.4% (95% CI: 57.1–99.8). Efficacy against
266 asymptomatic COVID-19 infections was 63.6% (29.0–82.4). In the 1858 elderly participants
267 in the analysis, the split of cases between vaccine and placebo groups was 5 (0.56%) of 893
268 participants and 16 (1.66%) of 965, respectively, giving an efficacy of 67.8% (8.0–90.0).
269 Efficacy in the 15,115 participants who were younger than 60 years was 79.4% (66.0–88.2)
270 (**Table 2**).

271 *Immune Responses*

272 At day 56 in the groups who received lots 1, 2, 3 or placebo GMTs (MNT₅₀) of SARS-CoV-2
273 neutralising antibodies were 130.3 (95% CI: 105.8–160.4), 121.2 (97.6–150.5), 125.4
274 (101.3–155.1), and 13.7 (10.7–17.4), respectively (**Table 4**). GMT ratios between all three
275 pairs of lots were consistently similar: lots 1:2 GMT ratio 1.08 (95% CI: 0.80–1.45), lots 1:3
276 GMT ratio 1.04 (0.77–1.40), and lots 2:3 GMT ratio 0.97 (0.71–1.31). All the 95% CIs for
277 the GMT ratios were contained within the interval [0.50, 2.0] (*Supplementary figure 1, page*
278 *11*), meeting the predefined criterion for a consistent immune response across lots.

279 There were no marked differences in GMTs for neutralizing antibodies at Day 56 when
280 assessed based on age or gender (*Supplementary table 3, page 12*). The GMT was higher
281 (194.3 [95% CI: 134.4–280.9, n = 48]) in vaccinees who were seropositive for SARS-CoV-2
282 IgG at baseline than in those who were seronegative (118.0 [104.0–134.0]).

283 At Day 56 IgG titres to all three epitopes (S1 protein, RBD, and N protein) were detected
284 after two doses. For all three lots combined the GMTs at Day 56 were 9742 EU/mL (95% CI:
285 8949–10606) for S1 protein, 4124 EU/mL (3731–4557) for RBD-competitive binding, and
286 4161 EU/mL (3736–4633) for SARS-CoV-2 N protein assays (**Table 4**). The placebo group
287 did not display any meaningful change in titres over the course of the study for any of the
288 immune targets.

289 *Safety*

290 There were 15 deaths in the study, none of which were considered by the investigators to be
291 related to the vaccine or placebo; six deaths were reported to be related to COVID-19. In
292 BBV152 recipients there were five deaths all due to causes unrelated to vaccination:
293 cerebellar haemorrhage, haemorrhagic stroke, ovarian cancer with metastases, sudden cardiac
294 death, and COVID-19. Ten placebo recipients died, also from unrelated conditions: alcohol
295 overdose, myocardial infarction, cardiac arrest with underlying hypertension, five from
296 COVID 19 and two which remain to be determined. No anaphylactic events were reported.

297 The vaccine had a good reactogenicity profile with similar rates of solicited, unsolicited, and
298 serious adverse events and adverse events of special interest in vaccine and placebo groups.
299 Serious adverse events occurred in 99 participants; 39 (0·30%) received BBV152 and 60
300 (0·47%) received placebo (*Supplementary Table 4, page 13*). Two related serious adverse
301 events were reported among BBV152 recipients. Long-term safety monitoring will continue
302 for 1 year after administration of the first dose of BBV152.

303 Solicited adverse events analyses are provided for all enrolled 25,798 participants
304 (*Supplementary table 5, page 14*). Overall, incidence rates were lower after the second dose
305 than the first, and tended to be slightly higher in the BBV152 group than the placebo group.
306 However, all incidence rates were low, with only 12·4% reporting any solicited AE after

307 vaccine or placebo. Among the local or systemic solicited AEs, only local injection pain was
308 reported with an incidence greater than 1% (*Supplementary table 4, page 13*). Similar
309 proportions of vaccine (3.04%) and placebo (2.78%) groups reported local pain after the first
310 dose, falling to 1.81% and 1.62% after the second dose, respectively. Other local AEs were
311 reported by less than 0.3% of participants in any group after either dose. Solicited systemic
312 AE were reported less frequently, after 2.57% and 1.92% of first doses of vaccine or placebo,
313 respectively. The most frequent solicited systemic AE overall was headache, followed by
314 pyrexia, fatigue and myalgia but at incidences below 1% in both groups. Rates of local and
315 systemic AEs reported in the BBV152 group as mild (11.2%), moderate (0.8%), or severe
316 (0.3%) were comparable to the placebo group (mild [10.8%], moderate [1.1%], and severe
317 [0.4%]). Unsolicited AEs were reported by 1.8% and 1.7% of vaccinees and placebo
318 recipients, respectively. No significant differences were observed between the vaccine and
319 placebo groups, the P value for all comparisons being > 0.05.

320 **DISCUSSION**

321 We report findings from the phase 3 efficacy, safety and immunogenicity clinical trial of
322 BBV152, a whole-virion inactivated SARS-CoV-2 vaccine. In the final per-protocol analysis,
323 measured 14 days after the second of two doses of BBV152, there was a vaccine efficacy of
324 77.8% (95% CI: 65.2–86.4) against symptomatic COVID-19 disease, and perhaps more
325 importantly a higher efficacy against severe COVID-19 of 93.4% (57.1–99.8). Thus, cases of
326 severe disease which require hospitalisation and have threatened to overwhelm healthcare
327 facilities will be markedly decreased in fully vaccinated populations Although the study was
328 not powered to definitively assess efficacy in subgroups with different ages, gender, or the
329 presence of pre-existing comorbid conditions, efficacy rates for symptomatic COVID-19
330 were all high in these sub-groups (>66%) with the lower limits of the respective 95% CIs
331 being above 30% in all cases except for the > 60 years group.

332 This phase 3 study confirms our earlier observations on the safety and immunogenicity
333 profiles of BBV152 in phase 1 and 2 trials [5,6]. There were no safety concerns raised, no
334 reports of anaphylactic events after BBV152 administration, and all adverse events (solicited,
335 unsolicited, and serious adverse events) were well balanced between BBV152 and placebo
336 groups. One possibly related serious adverse event in the BBV152 group was a case of
337 immune thrombocytopenic purpura that occurred 39 days after the second dose in a participant
338 who was SARS-CoV-2 seropositive at baseline, which resolved in four days. After any dose,
339 the combined incidence rate of local and systemic adverse events in this study is noticeably
340 better than the rates for other SARS-CoV-2 vaccine platform candidates [10,11], and
341 comparable to the rates for other inactivated SARS-CoV-2 vaccine candidates [12].

342 When measured as neutralising antibodies, the three consecutive manufacturing lots of
343 vaccine induced consistent humoral immune responses, and when measured as ELISA IgG
344 responses against three SARS-CoV-2 epitopes (S1 and RBD of the spike protein, and the
345 nucleocapsid antigen) antibody titres were similar across all lots (**Table 4**). Further, BBV152
346 generated comparable neutralising immune responses in participants < 60 and ≥ 60 years of
347 age (*Supplementary table 3, page 12*); vaccine efficacy was 79.4 % (95% CI: 66.0–88.2) and
348 67.8% (8.0–90.0) in the younger and older subgroups, respectively (**Table 2**).

349 The recent surge in SARS-CoV-2 variant strains has raised concerns regarding the efficacy of
350 vaccines against the new Variants of Concern (VoC). Some COVID-19 vaccines, notably
351 Coranavac and ChAdOx1, have been reported to have diminished efficacy against the
352 Gamma (P1) and Beta (B.1.351) variants first isolated in Brazil and South Africa [11,13].
353 The ChAdOx1 vaccine is reported to have equivalent efficacy against the Alpha (B.1.1.7)
354 variant, which is widely circulating [14]. Effectiveness after two doses of the mRNA-based
355 vaccine, BNT162b2, decreased from 93.4% (95% CI: 90.4–95.5) against B.1.1.7 to 87.9%
356 (78.2–93.2) against B.1.617.2 [15]. With ChAdOx1 effectiveness after two doses decreased

357 from 66.1% (54.0–75.0) against B.1.1.7 to 59.8% (28.9–77.3) against B.1.617.2 [15]. The
358 emergence of VoC occurred during the conduct of our trial, and we obtained additional
359 consent to collect additional NP swabs from RT-PCR-confirmed symptomatic COVID-19
360 participants. All sequences were generated by the National Institute of Virology, Pune, India
361 using the quantitative approach [16,17]. Controls were checked to ensure no evidence of
362 amplification in the negative tests and that expected RNA quantification was consistent with
363 cycle threshold (Ct) values provided by the testing laboratories. All samples were processed
364 by laboratory staff masked to vaccine allocation. A total of 79 variants were reported from
365 16,973 samples, 18 in the vaccine and 61 in the placebo group. Among 50 Delta (B.1.617.2)
366 positive-confirmed cases, 13 and 37 participants were in the vaccine and placebo arms,
367 resulting in vaccine efficacy of 65.2% (95% CI: 33.1–83.0). In breakthrough symptomatic
368 Delta variant infections, based on Ct values, the viral load in the vaccine arm was
369 significantly lower than the placebo arm. Efficacy against the Kappa (B.1.617.1) variant was
370 90.1% (95% CI: 30.4–99.8). No cases of severe variant-related cases of COVID-19 were
371 reported in the vaccinees but four severe cases were reported in the placebo recipients
372 infected with Alpha, Kappa, Delta, and unclassified variants respectively (Table 3). As
373 previously reported BBV152-induced antibodies show no significant decrease in
374 neutralisation activity against the Alpha (B.1.1.7) variant, but demonstrate marginal
375 reductions in neutralisation activity, by 2-, 2-, 3-, and 2.7-fold, respectively, of the B.1.1.28,
376 B.1.617.1, B.1.351 (Gamma), and B.1.617.2 (Delta) variants [18–21].

377 No licensed SARS-CoV-2 vaccine has reported efficacy against asymptomatic infection in a
378 randomised controlled trial, based on nucleic acid testing, although the mRNA vaccine,
379 BNT162b2, has been associated with decreased asymptomatic SARS-CoV-2 infections in
380 healthcare workers [22]. Several other vaccine studies employed surrogate markers to assess
381 asymptomatic efficacy by periodically collecting serum from trial participants and assessing

382 for anti-SARS-CoV-2-nucleocapsid binding antibody (N antigen) [10]. In this study, a total
383 of 8,721 participants made monthly clinical visits for routine medical check-ups and
384 collection of NP swabs for PCR confirmation of asymptomatic COVID-19. In the per
385 protocol set, 3,248 and 3,041 participants in BBV152 and placebo groups, respectively, were
386 enrolled and as per the cut-off date, up to two months after the second dose, 14 and 33
387 positive PCR confirmations have been reported in the vaccine and placebo groups,
388 respectively, an efficacy of 66.6 % (95% CI: 23.7–80.4). A study with the ChAdOx1 vaccine
389 found no efficacy (3.8%) against asymptomatic infections, albeit direct comparisons cannot
390 be made as a surrogate serological marker was used [10]. Our findings corroborate well with
391 preclinical protective efficacy studies in hamsters and NHP, which reported lower and upper
392 airway protection against SARS-CoV-2 infection [3,4].

393 This study has several limitations. Due to the low number of cases reported between doses 1
394 and 2, we cannot calculate vaccine efficacy after a single dose. This report contains a median
395 safety follow-up of 146 days for all participants, so long-term safety follow-up of BBV152 is
396 required and is currently underway. The data presented on efficacy against variants other than
397 Delta must be considered preliminary as the numbers reported are small. Additional efforts to
398 assess the clinical efficacy of BBV152 against VoC are being planned. The potential
399 establishment of a correlate of protection is not feasible at the time of this report. Finally, this
400 study population lacked ethnic and racial diversity, underscoring the importance of
401 evaluating the efficacy of BBV152 in other populations.

402 Although the study was designed to vaccinate and follow participants for one year after the
403 second dose, given the nature of the pandemic in India and the emergency use authorization
404 for BBV152, after meeting the pre-defined efficacy success criteria, the DSMB and sponsor
405 decided to unblind those placebo participants who were eligible to receive an approved
406 COVID-19 vaccine. Unblinding in such cohorts was planned only after the accrual of the

407 protocol pre-specified 130 cases, in a phased manner: health care professionals, individuals
408 ≥ 45 years, followed by those < 45 years. Our sample estimations accounted for 20%
409 seropositivity. As we observed baseline seropositivity rates of 30% and due to the unblinding
410 of the health care professionals and elderly individuals (who are eligible for COVID-19
411 vaccination), the protocol was amended to expand the sample size to 30,800, with 5,000
412 additional participants now being enrolled in Brazil. This will ensure the study evaluates the
413 efficacy of BBV152 against VoC and provides an opportunity to accrue additional severe
414 COVID-19 cases as well as more racial diversity. This manuscript contains data from the
415 Indian cohort only.

416 However, this study does have several strengths. The study enrolled participants with ages
417 ranging from 18 to 98 years and found no major differences in immune responses across the
418 broad age groups of under- and over-60 year-olds. Participants considered to be at-risk of
419 acquiring COVID-19 were prioritised, so a total of 2,750 participants were above 60 years of
420 age and 7,065 reported at least one pre-existing medical condition across ages. To ensure
421 generalisability, this study was conducted with participants from diverse geographic
422 locations, enrolling 25,798 participants across 25 hospitals. This is the first trial to report
423 preliminary promising findings on the efficacy against asymptomatic infections and clinical
424 lot-to-lot immunological comparability.

425 The most common solicited adverse event was pain at the injection site, followed by
426 headache, fatigue, and fever. No severe or life-threatening (Grade 4 and 5) solicited adverse
427 events were reported. Although the study was not powered to find such differences, no
428 meaningful safety differences were observed between the groups. After any dose, the
429 combined incidence rate of local and systemic adverse events in this study is noticeably
430 better than the rates for other SARS-CoV-2 vaccine platform candidates [23–27] and
431 comparable to the rates for other inactivated SARS-CoV-2 vaccine candidates [28,29].

432 However, other vaccine studies enrolled different populations and employed varying
433 approaches to measure adverse events.

434 The positive safety, immunogenicity and efficacy results presented here will support
435 regulatory submissions for emergency use authorisation (EUA) which BBV152
436 (COVAXIN™) has already received in 23 countries. With the inclusion of Vaccine Vial
437 Monitor 7, storage at 2°C–8°C, and a 28-day open-vial policy (limiting open-vial vaccine
438 wastage by 10–25%), the established efficacy of BBV152 against symptomatic and
439 asymptomatic infection will be critical towards mitigating the COVID-19 pandemic.

440

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453 **Author Contributions**

454 All authors met the criteria for authorship set forth by the International Committee for
455 Medical Editors. RE contributed to the manuscript preparation and KMV, SPr, KE, WB, NG,

456 SPa, PA, and BB reviewed the manuscript. RE and KMV and were responsible for overall
457 project coordination. SRe, VS, and VA were led clinical operations and helped immensely
458 with designing the protocol. WB was involved with the study design and statistical analysis
459 plan. VP, PY, and GS led the virological confirmation and genomic sequencing efforts. The
460 contract research organisation (IQVIA) was responsible for analysing the data and generating
461 the report. All principal investigators (SK, SR, PRe, SV, CS, SR, SM, AP, PRa, RG, MM,
462 SM, PB, and LK) were involved in the scientific review of this paper. RE, KMV, PY, GS,
463 VA, and VS had full access and verified the masked data in the study, and can vouch for its
464 accuracy and completeness. All authors had final responsibility for the decision to submit for
465 publication.

466 **Competing Interests**

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472 SR, PRe, SV, CS, SR, SM, AP, PRa, RG, MM, SM, PB, and LK were principal investigators
473 representing the study sites.

474 **Data Sharing Statement**

475 The study protocol is provided as *Supplementary Appendix 2*. Individual participant (de-
476 identified) data will be made available when the trial is complete upon direct request to the
477 corresponding author with an appropriate research proposal. Once such a proposal is
478 approved data will be shared through a secure online platform.

479

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562 safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials.
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- 564

565 **Table 1:** Demographic of participants in the safety population

566

Parameter	BBV152 n (%)	Placebo n (%)
N =	12,879	12,874
Age, years		
(Mean ± SD)	40·1 ± 13·8	40·1 ± 14·1
Range	18, 92	19, 97
Sex, n (%)		
Female	4214 (32·7)	4254 (33·0)
Male	8665 (67·3)	8620 (66·9)
Body Mass Index (BMI), kg/m²		
	24·3 ± 4·4	24·3 ± 4·3
Pre-existing medical conditions, n (%)		
Stable cardiovascular disease	557 (4·3)	523 (4·1)
Stable respiratory disease	126 (1·0)	170 (1·3)
Controlled diabetes	706 (5·5)	735 (5·7)
Stable liver disease	25 (0·2)	28 (0·2)
Severe obesity (BMI > 35)	56 (0·4)	94 (0·7)
Other stable co-morbidities	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)

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

571

572 **Table 2:** Efficacy against SARS-CoV-2 after at least 14 days following a second dose of BBV152 vaccine in the per protocol population.

Efficacy Endpoint	Total cases	BBV152	Placebo	Vaccine efficacy (CI)*
	n/N (%)	n/N (%)	n/N (%)	
Symptomatic COVID-19	130/16973 (0.77)	24/8471 (0.28)	106/8502 (1.25)	77.8 (65.2–86.4)
Severe Symptomatic COVID-19	16/16973 (0.09)	1/8471 (0.01)	15/8505 (0.18)	93.4 (57.1–99.8)
Symptomatic COVID-19 in participants 18–59 years	109/15115 (0.72)	19/7578 (0.25)	90/7537 (1.19)	79.4 (66.0–88.2)
Symptomatic COVID-19 in participants ≥ 60 years	21/1858 (1.13)	5/893 (0.56)	16/965 (1.66)	67.8 (8.0–90.0)
Symptomatic COVID-19 in participants with a pre-existing medical condition	49/4846 (1.01)	12/2328 (0.52)	37/2518 (1.47)	66.2 (33.8–84.0)
Asymptomatic COVID-19	47/6289 (0.73)	13/3248 (0.40)	33/3041 (1.09)	63.6 (29.0–82.4)
Symptomatic and asymptomatic COVID-19	75/6289 (1.19)	19/3248 (0.58)	56/3041 (1.84)	68.8 (46.7–82.5)

573 * 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
574 per protocol population, including randomly assigned participants who were seronegative at baseline and received two doses of either vaccine or placebo,
575 and remained on study at least 14 days after their second dose with no previous virologically-confirmed SARS-CoV-2 infection. COVID-19 cases were
576 defined as occurring in participants who had at least two of the following symptoms: fever (temperature $\geq 38^{\circ}\text{C}$), chills, myalgia, headache, sore throat, or
577 a new olfactory or taste disorder, or as occurring in those who had at least one respiratory sign or symptom (including cough, shortness of breath, or
578 clinical or radiographic evidence of pneumonia) and at least one nasopharyngeal swab that was PCR positive for SARS-CoV-2.
579

580 **Table 3:** Efficacy against variants of interest (VoI) and concern (VoC).

Variants (VoC/VoI)	Total number of cases n/N (%)	BBV152 n/N (%)	Placebo n/N (%)	Vaccine efficacy (CI)*
All variant related COVID-19	79/16,973 (0.47)	18/8471 (0.21)	61/8502 (0.72)	70.8 (50.0–83.8)
B.1.617.2 (Delta)	50/16,973 (0.29)	13/8471 (0.15)	37/8502 (0.44)	65.2 (33.1–83.0)
B.1.617.1 (Kappa)	11/16,973 (0.06)	1/8471 (0.01)	10/8502 (0.12)	90.1 (30.4–99.8)
B.1.1.7 (Alpha)	4/16,973 (0.02)	1/8471 (0.01)	3/8502 (0.04)	--
Other	14/16,973 (0.08)	3/8471 (0.04)	11/8502 (0.13)	73.0 (-2.2–95.2)
All variant related severe COVID-19	4/16,973 (0.02)	0/8471 (0)	4/8502 (0.04)	--
Ct values	All cases	BBV152 Mean	Placebo Mean	Mean difference of BBV152 – Placebo [95% CI]
B.1.617.2 (Delta) – E gene	20.11	25.55	18.20	1.42 (1.28–1.57)
B.1.617.2 (Delta) - ORF gene	22.97	28.29	21.09	1.35 (1.24–1.46)
All variants – E gene	20.44	24.01	19.38	1.24 (1.14–1.36)
All variants - ORF gene	23.26	26.55	22.29	1.19 (1.10–1.28)

581 Data include per protocol population only. In those participants who met the definition for symptomatic COVID-19 and were PCR positive an additional
582 nasopharyngeal swab for genotyping was collected. No viable sequence obtained or unprocessed due to cycle threshold (Ct) >30. Other pangolin lineages
583 detected include D614G (n = 7), B.1.36 (n = 3), B.1.1.419 (n = 1), B. 1.153 (n = 1), B. 1. 351 and B.1.618 (n = 1 each in placebo), and A (n = 1). The > 1
584 lower bound of 95% CI for mean ratio indicates a statistical significance; in breakthrough symptomatic Delta variant infections the viral load in the vaccine
585 arm was significantly lower than the placebo arm. We failed to retrieve the complete genome from 6 swab samples (all in placebo) subjected to sequencing.
586

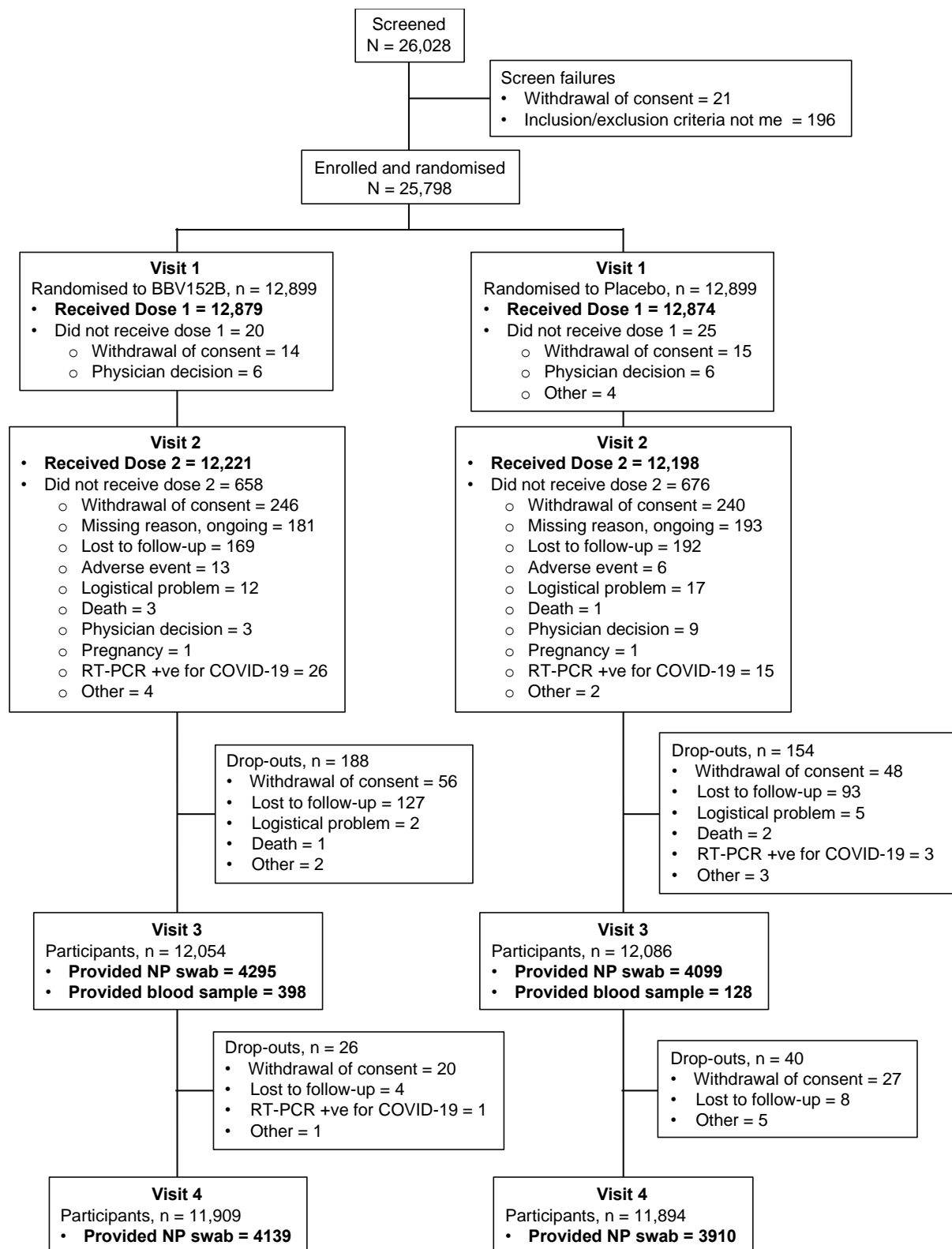
587 **Table 4:** SARS-CoV-2 neutralising (MNT₅₀) and binding antibody responses (Anti-S1 protein, RBD-binding, and N protein IgG). Data are shown for
588 neutralising response expressed as MNT₅₀ at Days 0 (baseline) and Day 56, four weeks after the second vaccination. Day 56 IgG antibody titres are
589 expressed as arbitrary ELISA units, all baseline titres being at the cut-off for the assay (reciprocal of 1:500 dilution).

Assay		Geometric mean titres (95% CI) at Day 56 in sub-sets of the different study groups				
		BBV152				Placebo
		Lot 1	Lot 2	Lot 3	All lots	
SARS-CoV-2 MNT ₅₀	N =	132	129	136	397	125
	Day 0	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)
SARS-CoV-2 MNT ₅₀	N =	128	125	133	386	119
	Day 56	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)
S-protein binding IgG	N =	129	124	134	387	121
	Day 56	9760 (8483, 11228)	10404 (8873, 12198)	9152 (7912, 10586)	9742 (8949, 10606)	1528 (1323, 1765)
RBD-binding IgG	N =	129	124	134	387	121
	Day 56	4266 (3584, 5079)	4423 (3669, 5333)	3740 (3180, 4399)	4124 (3731, 4557)	1443 (1261, 1651)
N protein binding IgG	N =	129	124	134	387	121
	Day 56	4551 (3800, 5450)	4183 (3423, 5111)	3798 (3165, 4558)	4161 (3736, 4633)	1485 (1275, 1730)

590

591 **Figure 1: CONSORT Flow Diagram**

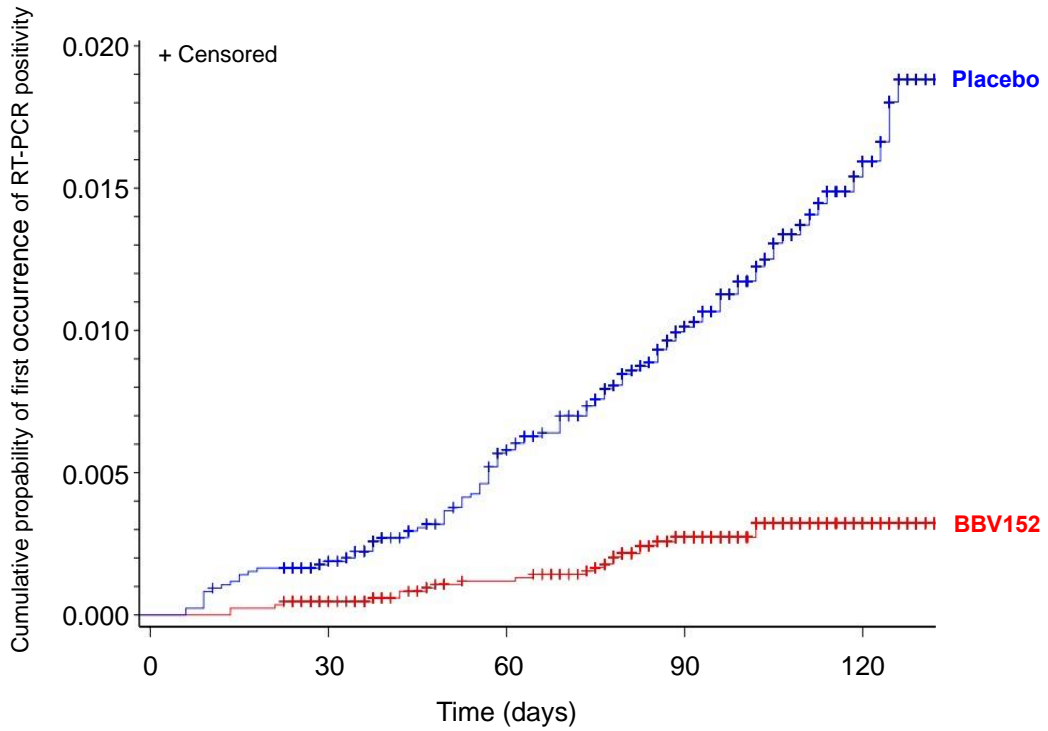
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594

595 **Figure 2:** Kaplan Meier plot of first occurrence of virologically confirmed (RT-PCR positive)
596 symptomatic cases of COVID-19 (per-protocol set)



597

598