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# A double-blind, randomised phase III clinical trial to evaluate safety, immunogenicity, non-inferiority & lot to lot consistency of single component oral cholera vaccine BBV131 (Hillchol®) in comparison to Shanchol™

Krishna Mohan Vadrevu [a,*], Abhishek Chavan [b], Amit Chawla [c], B.S. Chakravarthy [d], Chandramani Singh [e], Sagar Redkar [f], Savita Verma [g], Sriharsha Yandapally [h], M. Suma Priya [i], Vasant Khalatkar [j], Vishal Tripathi [k], Brunda Ganneru [a], Siddharth Reddy [a], Bhargav Reddy [a], Jan Holmgren [l], Badri Patnaik [a], Sai D. Prasad [a], Raches Ella [a]

[a] *Bharat Biotech International Limited, Hyderabad, India*
[b] *Jeevan Rekha Hospital, Belagavi, Karnataka, India*
[c] *Prakhar Hospital, Kanpur, Uttar Pradesh, India*
[d] *King George Hospital, Vizag, Vishakapatnam, Andhra Pradesh, India*
[e] *All India Institute of Medical Sciences, Patna, Bihar, India*
[f] *Redkar Hospital and Research Centre, Pernem, Goa, India*
[g] *Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, India*
[h] *Induss Hospital, Hyderabad, Telangana, India*
[i] *Malla Reddy Narayana Multispeciality Hospital, Hyderabad, Telangana, India*
[j] *Khalatkar Hospital, Nagpur, Maharashtra, India*
[k] *Rana Hospital, Gorakhpur, Uttar Pradesh, India*
[l] *Institute of Biomedicine, Department of Microbiology and Immunology, University of Gothenburg, Sweden*

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ABSTRACT

*Background:* Cholera is a vaccine-preventable disease that has faced a surge in outbreaks and a shortage of vaccines. The new generation oral cholera vaccine (OCV) BBV131, featuring a simplified single stable O1 Hikojima strain, aims to enhance production efficiency and affordability. This study evaluates BBV131's immune profile, safety, and non-inferiority compared to Shanchol™ in healthy adults and children. Adding BBV131 to the vaccine stockpile could improve supply, simplify logistics, and ease administration efforts.

*Methods:* In this randomised, modified, double-blind, multi-centre, phase III trial, 1800 participants were recruited across 10 clinical trial sites across India. Participants were stratified into three age groups (adults >18 years, children ≥5 to <18 years, and infants ≥1 to <5 years) and were randomised in a 3:1 ratio to receive either BBV131 or Shanchol™. All participants received two doses of the vaccine orally on days 0 and 14. Immunogenicity was assessed through blood samples collected at baseline, two weeks after each dose, and follow-ups at days 28, 56, 90, and 180. The primary endpoint focused on the proportion of participants achieving >4-fold increase in vibriocidal antibody titres against Ogawa and Inaba serotypes 14 days post two doses. While secondary endpoints included Geometric Mean Titre (GMT) measurements and safety. Safety was evaluated throughout the study, reporting solicited and unsolicited adverse events (AEs). Another cohort of 1800 was added to the above study as an addendum to expand the safety database.

*Findings:* Of the 1800 enrolled participants, 1794 completed the study. Post-vaccination, the percentage of participants in the BBV131 group who exhibited a > 4-fold increase in anti-*V. cholerae* antibody titres were 68.25 % for Ogawa and 69.52 % for Inaba—demonstrating non-inferiority to Shanchol™, with a lower limit of 95 % CI above the non-inferiority margin. The safety profile revealed 257 AEs among 236 participants (13.1 %), with similar incidence across age groups and between vaccines; common AEs included dry mouth and headache.

* Corresponding author.
*E-mail address:* kmohan@bharatbiotech.com (K.M. Vadrevu).

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*Interpretation:* The findings indicate that BBV131 demonstrates non-inferior immunogenicity and comparable safety to Shanchol™ in healthy Indian adults and children, supporting its potential as an effective OCV. Clinical Trial Registration: CTRI/2022/01/039734.

## 1. Introduction

Cholera is a life-threatening dehydrating diarrhoeal disease that results from the consumption of food or water contaminated with *V. cholerae* bacteria. Of the 200 serogroups of *V. cholerae* available in nature, serogroups O1 and O139 are mainly responsible for causing the disease. *V. cholerae* O1 strains are further divided into two serotypes (e.g., Ogawa and Inaba) based on their phenotypic differences in O1 antigen. A transitional serotype, Hikojima, occurs during serotype switching from Ogawa to Inaba, however there is no evidence for the occurrence of stable Hikojima strains in nature [1–3]. *V. cholerae* has sparked seven pandemics, with the ongoing 7th pandemic beginning in 1961, underscoring the disease's status as both a global public health menace and a marker of insufficient social development [4–6]. Approximately, *V. cholerae* affects 1.3 to 4.0 million people per year, causing 21,000 to 143,000 deaths worldwide, predominantly in developing nations across Africa, Asia, and the Americas. Children under five years of age account for about half of all cases and deaths, although individuals of all ages are susceptible. WHO reported recently that the dynamics of cholera outbreaks are becoming increasingly complex, with a rise in the number of cholera cases, since 2021 [6,7]. Thus, highlights the escalating challenge of controlling *V. cholerae* infections & transmission.

Efforts for improving safe drinking water and sanitation systems, along with deployment of oral cholera vaccines (OCVs)— endorsed by WHO's "Ending Cholera – A Global Roadmap to 2030 [8–11]. They all contain the same heat- and formalin-inactivated *V. cholerae* O1 components of both Inaba and Ogawa serotypes and El Tor and classical biotypes; in addition, Dukoral contains recombinantly produced cholera toxin B subunit (rCTB) and the other two a formalin-inactivated *V. cholerae* O139 component [8]. These vaccines have demonstrated efficacy with the protective impact being further enhanced by herd protection; however, their multicomponent composition burdens production capacity and contributes to the current, severe global vaccine shortage.

The vaccine constructs strategy leverages the understanding that the immune response against the cholera targets the O1 lipopolysaccharide (LPS) and rCTB [12]. Antigenicity of *V. cholerae* is dependent on the protein-polysaccharide association, and these antigens are well-preserved after heat or formalin inactivation [13]. This suggests that a single inactivation method could suffice, with formalin being more practical for large-scale production. Moreover, non-existence of O139 for the last 25 years and reemergence of O1 serotype emphasizes the use of O1 serotype as a vaccine candidate. Hence, in-view of all the above, the formalin-inactivated Hikojima serotype *V. cholerae* O1 strain co-expressing the Inaba and Ogawa O1 antigens have been explored towards developing simplified, cost-effective, scalable & single-component OCVs [14].

Lebens et al. first described the construction of a formalin-inactivated Hikojima serotype *V. cholerae* strain to produce single component whole-cell OCV [15]. Later, Prof. Holmgren (University of Gothenburg, Gotovax AB, Sweden) and his team, optimized Hikojima serotype vaccine strain (El Tor biotype, MS1568), to express equal amounts of the Ogawa and Inaba LPS antigens on the cell surface and licensed to MSD-Wellcome Trust Hilleman Laboratories, India. Thus, led to development of Hillchol®, which is simplified, scalable and affordable OCV. Its immunogenicity and safety were established, showing non-inferiority to Shanchol™ in both preclinical and an early clinical trial in Dhaka, with no serious adverse events [16,17].

In 2021 Hilleman Labs partnered with Bharat Biotech International Ltd. (BBIL), India, for further GMP manufacturing scale-up, analytical and clinical development, and commercialisation of the OCV, (BBV131) which is free of thiomersal and other preservatives. To further improve storage, transport and accessibility and improved user experience, BBIL changed the presentation of the vaccine from conventional glass vials to respule (a small plastic container that contains a liquid).

BBIL conducted pre-clinical studies on Wistar rats and NZW rabbits confirmed BBV131's safety and immunogenicity (unpublished). As described here, a multicentre phase III clinical trial was conducted to evaluate the non-inferiority in terms of immunogenicity and safety of the candidate vaccine to the WHO-prequalified OCV Shanchol™ in healthy individuals aged >1 year in India and simultaneously the lot-to-lot consistency was also assessed. An additional single-arm safety study with 1800 participants was conducted to further evaluate the safety profile of BBV131.

## 2. Methods

### 2.1. Clinical trial design and participants

Current study is a phase III, randomised, modified double-blind, multicentric clinical trial, proposed to assess the immunogenicity and safety of BBV131 against Shanchol™ and also to evaluate lot-to-lot consistency across three batches of the investigational vaccine. This trial was approved by the National Regulatory Authority adhering to the New Drugs and Clinical Trials Rules, 2019. The trial was conducted between 19 May 2022 to 2 February 2023 in ten centres (*Supplemental Table 1*) that are geograpically located at different regions of India with varied status of endemicity [18,19], after obtaining ethical committee approvals from each centre and in compliance with International Council for Harmonization (ICH) Good Clinical Practice guidelines. The study was registered on two clinical trial registries (CTRI/2022/01/039734) and (NCT05507229).

A total of 1800 participants, were screened based on health status, ensuring a diverse demographic analysis and stratified into age cohorts of ≥18 years, ≥ 5 to <18 years, and ≥ 1 to <5 year, Participants with history of cholera vaccination or infection, hypersensitivity to past vaccinations, immune disorders, significant acute symptoms, or recent treatment for diarrhoea were excluded. All trial sites were tertiary care centres located in urban areas and the participants were enrolled after obtaining due informed consent. In case of minors, consent was obtained from parents or legal authorised representatives (LARs), with additional assent from those aged 12 to <18 years. In the context of a per-protocol analysis, participants who vomited after receiving a vaccine dose would be included in the analysis. To further evaluate safety, 1800 additional participants were enrolled to adverse events post two-dose BBV131, meeting WHO PQ requirements (CTRI/2023/01/049320). This addendum safety study was a single-arm clinical trial assessing BBV131's safety across various age groups: ≥18 years, ≥5 to <18 years, and ≥ 1 to <5 years. A total of 1800 healthy participants were evenly distributed among these groups and received two doses of the BBV131 vaccine on days 0 and 14. The primary focus was on monitoring safety post-immunization.

### 2.2. Vaccines

The BBV131 vaccine, is a formaldehyde-inactivated *V. cholerae* O1 E1 Tor Hikojima recombinant serotype MS1568, expressing approximately equal amounts of Ogawa and Inaba LPS, which was orally administered to participants using a 1.5 ml single oral dose respules with

vaccine formulated to contain ≥900 μg LPS per dose of O1 E1 Tor Hikojima serotype recombinant strain. Three cGMP batches (45A21004A, 45A21005A, and 45A21006A) were used in this study to evaluate the lot to lot consistency. The comparator vaccine, Shanchol™, (Shantha Biotechnics-Sanofi Pasteur; lot 2SCNO13A21) stored in 1.5 ml single oral dose vials, contains formalin-killed *V. cholerae* O139 bacteria and multiple inactivated *V. cholerae* O1 Classical and E1 Tor strains of Ogawa and Inaba serotypes, which are heat inactivated and formalin inactivated. Both vaccines stored at 2–8 °C before administration.

### 2.3. Randomisation and masking

Participants within each demographic cohort were randomly allocated in a 3:1 ratio to receive either BBV131 ($n = 450$) or Shanchol™ ($n = 150$), employing an Interactive Web Response System (IWRS) developed by the Contract Research Organization (CRO), IQVIA, prior to the commencement of the study for vaccine assignment on both Day 0 and Day 14 of the study. The system ensured an equitable distribution among the three lots of BBV131 in 1:1:1 ratio.

To preserve the integrity of the double-blind methodology, participants, investigators, and personnel involved in executing study-related assessments or collecting biological samples post-vaccination or sample testing were blinded to the group allocations and vaccine assignments.

Given the presentation characteristics of BBV131 (respules) and Shanchol™ (vials), an unblinded pharmacist at each study site was tasked with administering the investigational product (IP) to participants. This procedure was conducted in a designated setting to maintain blinding among the remaining study staff and participants. The unblinded pharmacist's role was strictly limited to vaccine dispensing, with no involvement in subsequent treatment or follow-up.

### 2.4. Study procedure

The study commenced with the recruitment of group I participants (aged ≥18 years), who were randomised to receive 1.5 ml of either BBV131 or Shanchol™ on day 0 and day 14. Following the administration ofvaccine, participants were observed for 30 min, post-vaccination, to assess immediate adverse events following immunization, if any. Solicited adverse events (local and systemic reactions) were also recorded for seven days post-vaccination. Follow-up for these solicited adverse events was actively pursued through daily telephone communications during the first week following each vaccination dose. Furthermore, any unsolicited adverse events and serious adverse events were reported throughout the trial. Adverse events were categorised based on severity (mild, moderate, or severe) and causality (related or unrelated) to the vaccine by the principal investigator at each participating site, as predefined in the Protocol.

An interim safety data review was conducted after seven days for the initial 40 participants. Upon evaluating the safety profile, data and safety monitoring board (DSMB), recommended to proceed with the recruitment of an additional 560 participants in group I and to initiate the enrolment for group II (aged 5 to <18 years) participants. This group subsequently underwent a similar procedure of randomisation, vaccination, and safety data review. Upon DSMB's approval, the study advanced to group III (aged 1 to <5 years), repeating the aforementioned sequential steps.

### 2.5. Blood samples

In this study, venous blood samples were collected from participants at multiple time points for immunogenicity assessment: at baseline (Day 0) and post-vaccination during follow-up visits on days 14, 28, 56, 90, and 180. Sera were separated and then stored at −80 °C for subsequent immunological analyses, specifically vibriocidal antibody assays.

### 2.6. Serological assays

#### 2.6.1. Vibriocidal antibody assay

The evaluation of immune responses to the *V. cholerae* O1 Inaba and Ogawa serogroups was conducted by measuring serum vibriocidal antibody levels against target strains (*V. cholerae* O1 Inaba and Ogawa serotypes) at Bharat Biotech, using established and validated standard testing procedures. [16,20,21]. The test was performed with two-fold serial dilutions of pre- and post-vaccination serum samples, using guinea pig complement (Cat No#C300–0050, Rockland Immuno chemicals, USA) and *V. cholerae* O1 E1 Tor Ogawa (Clinical isolate, Strain X-25049) and Inaba (Clinical isolate, Strain T-19479) strains as the target organisms. Clinical sera samples were run single in different dilutions. Assay variations were verified by including positive and negative controls in each plate. Rabbit hyperimmune sera (R1081, received from the Holmgren lab, University of Gothenburg, Sweden) was used as quality control reference. While, the rabbit hyper-immune sera raised in Bharat Biotech was used as an additional internal control, after internal qualification by comparing with Human convalescent sera, received from International Vaccine Institute, Seoul, South Korea**.** Negative controls (wells with serum and complement without bacteria; serum and bacteria without complement; saline and bacteria with complements; saline and bacteria without complement; and only saline) were included to meet the assay specifications. All samples were tested in a blinded manner. A CRO was engaged for unblinding the samples and data analysis. A subset of samples was also tested at the Holmgren lab **to** check the inter-laboratory variability, as a part of assay validation.

Anti-Ogawa and anti-Inaba vibriocidal titres were defined as the reciprocal of the highest serum dilution that gave a 50 % or greater reduction in optical density relative to control wells that do not contain serum.

### 2.7. Outcomes

The primary endpoint was to assess the potential non-inferiority across all age cohorts regarding the proportion of participants achieving seroconversion against Ogawa and Inaba at Day 28 (visit 3), when administered with BBV131 or the comparator vaccine. Seroconversion was defined as a 4-fold increase in individual vibriocidal titres obtained at post-vaccination (Day 28) compared to pre-vaccination (Day 0).

Secondary endpoints were to evaluate the immunogenicity and safety metrics for both vaccine arms. The immunogenicity of BBV131 with Shanchol™ was ascertained through the comparative analysis of geometric mean titres (GMTs) of anti-Ogawa and Inaba vibriocidal antibodies elicited two weeks post two-doses, in participants administered with BBV131 and those receiving Shanchol™. Safety parameters were quantitatively and qualitatively assessed and juxtaposed based on the frequency and severity of both solicited (local and systemic reactogenicity within 30 min and seven days after vaccination) and unsolicited adverse events (throughout the study) following the dispensation of two doses of the test and comparator vaccines across all demographic strata. An exploratory immunological endpoint was to demonstrate lot to lot consistency, based on the anti-ogawa and anti-Inaba vibriocidal titres.

### 2.8. Statistical analysis

We calculated a sample size of 1800 participants would provide around 90 % power to detect non-inferiority of seroconversion rates in BBV131compared with Shanchol™ in all ages combined (primary endpoint) and immune equivalence of three lots of BBV131 (secondary endpoint).

Based on a previous study of Hillchol® and Shanchol™ conducted in Bangladesh [17], we assume the standard deviation (SD) of log10(titre) is 0.66 for both serotypes. If the lower limit of two-sided 95 % CI of the

difference of seroconversion rates and GMT ratio of BBV131 and Shanchol™ were greater than the predefined non-inferiority margin of −10 % and 0·67, respectively, BBV131would be considered non-inferior. Assuming a one-tailed alpha of 2·5 % and a 10 % dropout rate, we estimated 1350 participants randomised to BBV131 (450 per age group) and 450 participants randomised to Shanchol™ (150 per age group). Allowing for 10 % loss due to withdrawal and other reasons, the expected sample size available for analysis was 405 participants per each age group of BBV131 [total of 1215 participants in BBV131 arm] and 135 participants per each age group of Shanchol™ [total of 405 participants in Shanchol™ arm].

The criterion for consistency of 3 lots of BBV131was two-sided 95 % CI for GMT ratio of any 2 lots had lower limit ≥0.667 and upper limit ≤1.5. The batch-wise comparison of GMTs of anti-Ogawa and anti-Inaba antibodies for BBV131group non-inferiority was that the two-sided 95 % CI for difference in seroconversion rates [rate for BBV131 ® minus rate for Shanchol™] had lower bound ≥ −10 %. The CI was calculated by a likelihood score method. Assuming a true seroconversion rate of 80 % for both BBV131and Shanchol™, the power to show NI was >99 % for Inaba and Ogawa separately; if the true rates were both 70 %, the power was approximately 97 %. If the true seroconversion rate for BBV131was 2 % lower than the rate for Shanchol™, the powers were reduced to approximately 95 % and 88 %, respectively.

Additionally, proportion of participants in terms of seroconversion with respect to vaccine antibody for each post dose 2 visit was summarised (percentages and 95 % CI using Clopper-Pearson method). The analysis populations were defined as follows: The Randomised Analysis Set (RAS) included all individuals randomised and vaccinated. The Intent-to-Treat Analysis Set (ITT) comprised all randomised participants with at least one post-vaccination measurement of anti-*V. cholerae* O1 Ogawa and O1 Inaba antibody titres. The Safety Analysis Set (SAS) encompassed all individuals randomised and vaccinated at least once.

Descriptive statistics are presented for baseline subject characteristics as well as data generated after randomisation. In general, for continuous variables, these statistics include n, mean, median, minimum, maximum, and standard deviation (SD); and for categorical variables these statistics include frequency and percentages.

Analyses was based on vibriocidal antibody titre after the second dose of vaccine: difference in seroconversion (SC) rates for non-inferiority (NI) and ratio of geometric mean titres (GMTs) for lot consistency. NI and lot consistency were assessed for the entire age range of study participants and for both the Ogawa and Inaba serotypes.

The primary immunogenicity endpoint was analysed in the per-protocol analysis set, which included all participants who received two vaccine administrations, had no important protocol deviations, and who provided blood samples for all immunogenicity assessments. The primary safety endpoint was assessed in all participants who received at least one dose of the BBV131or Shanchol™ vaccine. Lot-to-lot consistency was analysed in the full analysis set, which included all participants who received at least one dose of BBV131or Shanchol™ and provided at least one blood sample for immunogenicity assessment (modified intention-to-treat analysis). Missing immunogenicity data were not imputed for the analysis.

Comparisons of categorical outcomes, such as seroconversion, were conducted using the chi-square test or Fisher's exact test. Continuous parameter, like titres, were analysed using Student's *t*-test, where *p* value <0.05 was considered statistically significant.

95 % confidence intervals (CI) calculated using the likelihood method, focused on the primary endpoint. To establish NI between BBV131 and Shanchol™, the difference in seroconversion rates required a lower boundary of the 95 % CI of ≥ −10 % for both serotypes. Geometric Mean Titres (GMT) were summarised with SCR Difference and 95 % CIs. For BBV131 lot consistency, the two-sided 95 % CI for the GMT ratio of any two lots needed to be between ≥0.667 and ≤ 1.5. Safety endpoints included enumerating participants experiencing adverse events post-vaccination, with trial integrity and safety data reviewed by an independent board. Statistical analysis was performed using SAS® system Version 9.4.

## 3. Results

### 3.1. Study participants

Between 19 May 2022 and 02 August 2022, a multicentric, randomised, controlled trial was conducted across ten clinical trial sites, wherein 1806 individuals were screened for eligibility. Of these, 1800 participants met the eligibility criteria and were subsequently enrolled into three demographically stratified cohorts based on age: group I encompassed adults aged ≥18 years [*N* = 600], group II included children and adolescents aged ≥5 to <18 years [N = 600], and group III comprised toddlers aged ≥1 to <5 years [N = 600]. Participants within each cohort were randomised in a 3:1 ratio to receive either the investigational vaccine [*N* = 450] or the licensed comparator, Shanchol™ [*N* = 150]. All the 1800 randomised participants comprised the randomisation analysis set, intent-to-treat analysis set, and safety analysis set. Of these, the per-protocol analysis set included 1794 (99.7 %) participants – 599 (99.8 %) in group I, 597 (99.5 %) in group II, and 598 (99.7 %) in group III.

The trial achieved a completion rate of 99.0 % (*n* = 1782 participants), with a discontinuation rate of 1.0 % attributed to various non-serious reasons: 0.7 % (*n* = 13) withdrew consent unrelated to adverse events (AEs), 0.2 % (*n* = 4) were lost to follow-up due to migration, and 0.1 % (n = 1) discontinued for other unspecified reasons. Baseline demographic and clinical characteristics were statistically comparable between the two vaccine groups, ensuring validity in comparative analyses. No significant difference was found in age and sex distribution between the test and comparator vaccine in all age groups. (Table 1, Fig. 1).

### 3.2. Vibriocidal antibody responses

#### 3.2.1. Sero conversion rates

The population, comprising 99.7 % (*n* = 1794) of the participants, were analysed for seroconversion rates, and the data revealed robust immunogenicity across all age groups against both serotypes. (Table 2) Across the three age groups, 918 (68.25 %) participants in the BBV131 group vs. 305 (67.93 %) participants in the Shanchol™ group achieved seroconversion against Ogawa serotype 14 days after two doses of Test or Comparator Vaccine (Per Protocol Analysis Set). Similar results were achieved for the Inaba serotype, with 935 (69.52 %) seroconversion for BBV131 vs. 303 (67.48 %) for Shanchol™.

For age group I, BV131 demonstrated seroconversion rates of 69.11 % against Ogawa and 69.33 % against Inaba serotypes, compared to the Shanchol™ age group I group's 69.80 % for both serotypes. In age group II, BBV131 showed seroconversion rates of 67.11 % for Ogawa and 70.02 % for Inaba, slightly higher than Shanchol™ 66.67 % and 69.33 %, respectively. While in age group III revealed BBV131 with seroconversion rates of 68.53 % for Ogawa and 69.20 % for Inaba, surpassing Shanchol™ 's 67.33 % and 63.33 %, showing a consistent pattern of BBV131's effectiveness across different serotypes when compared to Shanchol™. Thus, in this study, the non-inferiority criterion – lower bound 95 % CI ≥ −10 % – was achieved in all age groups against both serotypes when comparing the test vaccine with Shanchol™ (Table 2, Fig. 2).

Further, studies over time of vibriocidal antibody seroconversion rates against Ogawa and Inaba among recipients of BBV131 and Shanchol™ likewise revealed no differences between the vaccines; for both vaccines and serotypes seroconversion rates declined by approximately 20 % from day 28 to day 180, from 68.3 to 68 % to 47.2–49.6 % for Ogawa and from 69.5 to 67.5 % to 50–47.8 % for Inaba (Fig. 2).

**Table 1**
Demographics characteristics of participants ($N = 1800$).

| Parameter | Statistics | Group 1 (Age: ≥18) (Total N = 600) | | *p-value | Group 2 (Age: ≥5 to < 18) (Total N = 600) | | *p-value | Group 3 (Age: ≥1 to < 5) (Total N = 600) | | *p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | BBV131 (N = 450) | Shanchol™ (N = 150) | | BBV131 (N = 450) | Shanchol™ (N = 150) | | BBV131 (N = 450) | Shanchol™ (N = 150) | |
| Age (Years) | n (%) | 450 (100) | 150 (100) | – | 450 (100) | 150 (100) | – | 450 (100) | 150 (100) | – |
| | Mean ± SD | 34.0 ± 10.32 | 33.0 ± 10.84 | 0.412 | 12.7 ± 3.46 | 12.9 ± 3.74 | 0.648 | 2.8 ± 1.09 | 2.6 ± 1.11 | 0.295 |
| | Median | 32 | 31 | – | 13 | 14 | – | 3 | 3 | – |
| | Min; Max | 18; 68 | 18; 69 | – | 5; 17 | 5; 17 | – | 1; 4 | 1; 4 | – |
| Sex, n (%) | Male | 307(68.2) | 92(61.3) | 0.146 | 237(52.7) | 86(57.3) | 0.335 | 255(56.7) | 92(61.3) | 0.343 |
| | Female | 143(31.8) | 58(38.7) | | 213(47.3) | 64(42.7) | | 195(43.3) | 58(38.7) | |
| Medical History Hypertension n (%) | | 0 (0.0) | 1 (0.7) | | 0 (0.0) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | |

Table 1: Data are Mean (SD) n (%), Median, Min; Max, participants who received at least one dose. % = n/N *100; n = number of subjects in the relevant population and N = Total number of subjects enrolled in the study. * Age was compared between treatment using the t-test, and Sex variables were compared using the Chi-square test where p-value <0.05 was considered statistically significant. All participants in this study were of South Asian descent.

### 3.2.2. Post- vaccination GMT responses

Overall GMT point estimates for anti-Ogawa and anti-Inaba antibodies at Day 0 were 33.9 and 20.7 for BBV131 vs. 29.7 and 25.1 for Shanchol™ groups, respectively. As illustrated in Fig. 3A post 2 doses, the GMT point estimates increased to 282.1 & 221.5 vs. 341.4 & 217.2 at Day 14 and sustained at 249.1 & 196.3 vs. 261.3 & 194.9 till Day 28 for BBV131 vs. Shanchol™ groups, respectively. Post Day 28, the GMT point estimates for anti-Ogawa and anti-Inaba antibodies declined over time to 71.9 and 64.5 vs. 83.6 and 71.0 on Day 180 in the study for the overall BBV131 vs. Shanchol™ groups, respectively and were not significantly different between the vaccines at any time point (Fig. 3). Despite this fall at Day 180, the antibodies remained twice as elevated as the baseline titres. Fig. 4 shows the GMT responses in the different age groups before vaccination and at two weeks after the first and the second dose. As for the combined age groups there were no significant differences either between the two vaccines or between the age groups or serotypes.

### 3.2.3. Lot-to-lot consistency

The batch-wise comparison of seroconversion rates and GMTs of anti-Ogawa and anti-Inaba antibodies for the BBV131 group are presented in Tables 3 and 4.

The number of participants achieving seroconversion 14 days after two doses who received vaccine lots 1, 2, and 3 of BBV131 (Per Protocol Analysis Set) were 295 (66 %), 312 (69.49 %) and 311 (69.27 %) respectively against Ogawa Serotype, and 319 (71.36 %), 296 (65.92 %) and 320 (71.27 %) respectively against Inaba serotype (Table 3).

The point estimates of GMT [95 % CIs] ratios for anti-Ogawa and anti-Inaba serotypes between all 3 lots of BBV131 (i.e., Lot 1 vs. Lot 2, Lot 1 vs. Lot 3, and Lot 2 vs. Lot 3) were consistently similar at Day 0, Day 14, Day 28 (Table 4) as well as at, Day 90 and Day 180 with the 95 % CIs for the GMT ratios within limit [≥0.667 and ≤ 1.5], thus, meeting the predefined criterion for consistent immune response across lots except Lot 1 vs. Lot 3 at Day 56 for anti-Ogawa antibodies and at baseline Day 0 values for Lot 1 vs. Lot 2 and Lot 1 vs. Lot 3 for anti Inaba antibodies.

Thus, point estimates of GMT [95 % CI] Ratios were comparable across the three lots of BBV131 for Day 0, Day 14, and Day 28 for anti-Ogawa and anti-Inaba antibodies.

The GMT ratios between all three pairs of lots were within the predefined margin. For lots 1 and 2, the ratio was 0.94 (95 % CI 0.75–1.17) for Ogawa and 0.97 (95 % CI 0.76–1.23) for Inaba. For lots 1 and 3, the ratio was 0.97 (95 % CI 0.78–1.21) for Ogawa and 0.95 (95 % CI 0.75–1.19) for Inaba. Lastly, for lots 2 and 3, the ratio was 1.04 (95 % CI 0.84–1.29) for Ogawa and 0.98 (95 % CI 0.77–1.23) for Inaba.

### 3.3. Safety

The safety cohort included 1800 participants from all three age groups (group I-600, group II-600, and group III-600). A total of 257 AEs was reported from 236 (13.1 %) participants, of which 200 AEs in 180 (13.3 %) participants from the BBV131 group and 57 AEs in 56 (12.4 %) participants from the Shanchol™ group. The AE incidence was similar across the different age group I, II, and III were comparable for the BBV131 and Shanchol™ arms. None of the participants vomited within 30 mins of vaccination.

In group I, group II and group III 68 AEs in 61 (13.6 %) participants from BBV131 arm, and 17 AEs from 16 (10.7 %) participants from Shanchol™ arm; 74 AEs in 66 (14.7 %) participants from BBV131 arm, and 21 AEs from 21 (14.0 %) participants from Shanchol™ arm and 58 AEs in 53 (11.8 %) participants from BBV131 arm, and 19 AEs from 19 (12.7 %) participants from Shanchol™ arm respectively.

A total of 203 solicited AEs was reported from 196 (10.9 %) participants during the entire study period – 157 solicited AEs in 151 (11.2 %) participants from the BBV131 group and 46 solicited AEs in 45 (10.0 %) participants from the Shanchol™ group. Of these 203 solicited AEs, 75 were local solicited AEs from 75 (4.2 %) participants, and 128 were systemic solicited AEs from 124 (6.9 %) participants during the entire study period. All the solicited AEs were considered related to the study intervention. A total of 54 unsolicited AEs was reported from 46 (2.6 %) participants in the study – 43 unsolicited AEs in 35 (2.6 %) participants from the BBV131 group and 11 unsolicited AEs in 11 (2.4 %) participants from the Shanchol™ group. The incidence of solicited and unsolicited AEs was similar across participants receiving BBV131 or Shanchol™ across study groups I, II, and III.

Of the total 257 AEs reported in the entire study from 236 (13.1 %) participants, 216 AEs in 206 (11.4 %) participants were considered related to the vaccine – 167 AEs in 158 (11.7 %) participants of the BBV131 arm and 49 AEs in 48 (10.7 %) participants of Shanchol™ arm. The common 'related' AEs (occurring in ≥1 % overall participants) were oropharyngeal pain [1.9 % overall; 2.0 % in BBV131 and 1.8 % in Shanchol™ arms], dry mouth [1.8 % overall; 1.9 % in BBV131 and 1.6 % in Shanchol™ arms], nausea [1.4 % overall; 1.5 % in BBV131 and 1.3 % in Shanchol™ arms], headache [1.2 % overall; 1.0 % in BBV131 and 2.0 % in Shanchol™ arms], vomiting [1.1 % overall; 1.4 % in BBV131 and 0.2 % in Shanchol™ arms], and cough [1.1 % overall, 1.1 % in BBV131 and 1.1 % in Shanchol™ arms], with a comparable incidence across the study group I, II and III, and similar between the BBV131 and Shanchol™ arms for the overall as well as group-wise participants.

In a study comparing BBV131 and Shanchol™ vaccines, 54 unsolicited adverse events (AEs) were reported in 46 (2.6 %) of participants, with the most common being pyrexia (1.1 %) followed by diarrhoea (0.5 %), nasopharyngitis (0.3 %), headache (0.3 %), and cough (0.2 %). 13

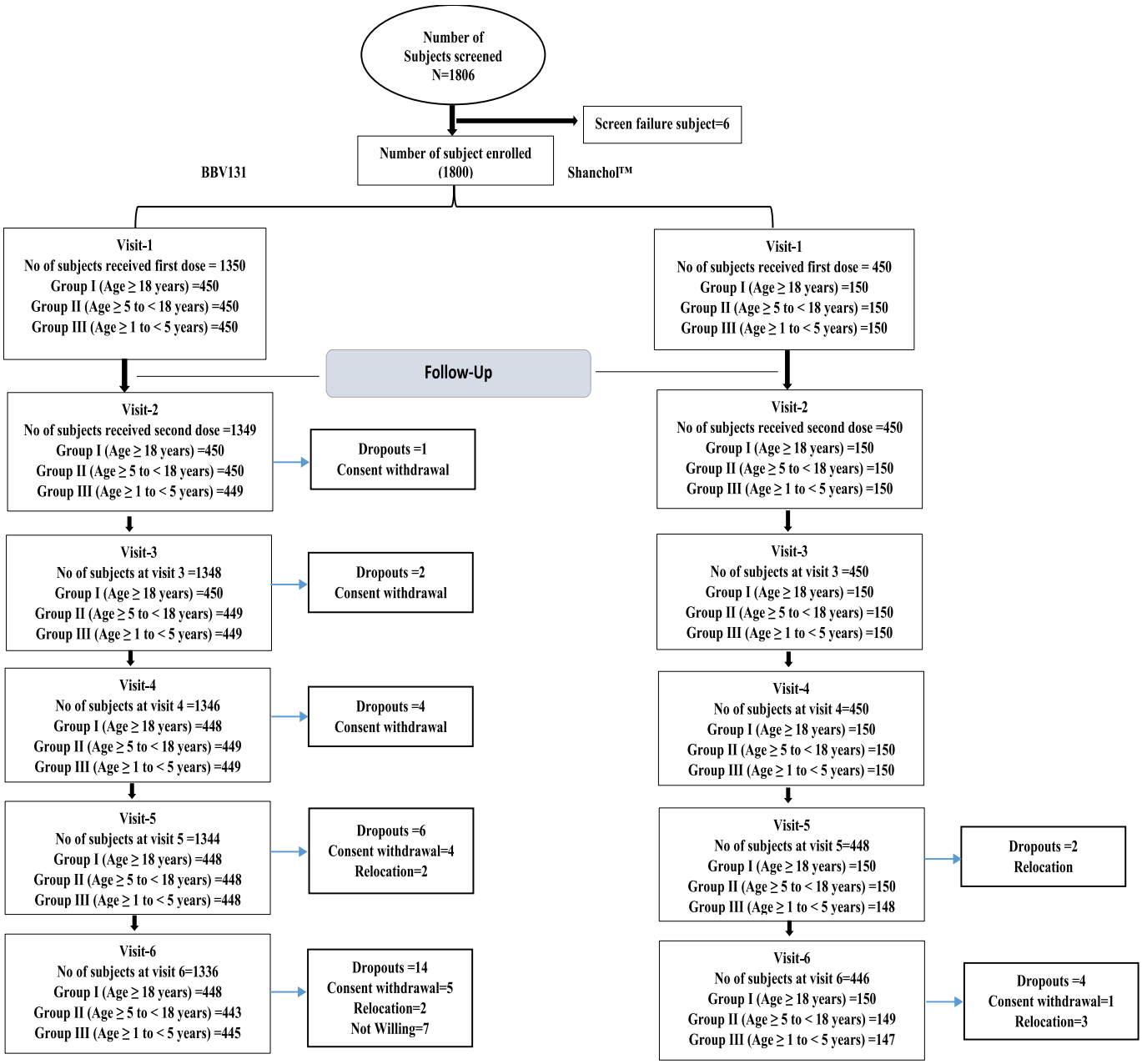


**Fig. 1.** Trial Profile.

AEs in 12 (0.7 %) participants were deemed vaccine-related, occurring at similar rates across both groups. All unsolicited AEs during the 14-day follow-up were mild, and no major differences were noted between vaccine arms.

All the 257 AEs reported in the study were considered resolved by the end of the study. There was no change in dose, study intervention interruption or withdrawal, increase in dose, or reduction in dose required due to any AEs for any participant in the study. There were no reports of any medically attended AEs (MAAEs), AE of special interest (AESI), serious adverse events (SAEs), or AEs leading to discontinuation or death from any participant in the study. Vaccination with BBV131 was well-tolerated, with no unexpected safety concerns raised throughout six months post-vaccination. BBV131 vaccine exhibited a good reactogenicity profile, and the overall adverse event profile (including solicited and unsolicited events) was well-balanced and comparable between investigational vaccine and Shanchol™ arms for all the study age groups (Table 5 **and** Table 6).

In addition to the above mentioned safety, Immunogenicity and Lot-to- Lot Consistency study, an additional cohort of 1800 participants across three age groups: group I (600 participants), group II (600 participants), and group III (600 participants) were recruited in single BBV131 arm to analyse the safety profile in an extended study population. Safety profile is similar as in the previous cohort. Out of 1800 participant**s,** a total of 258 adverse events (AEs) were reported, involving 240 participants (13.33 %) across the different age groups. Specifically, there were 91 AEs reported in participants aged 18 years and above, 81 AEs in those aged 5 to under 18 years, and 86 AEs in children aged 1 to under 5 years. Among these, 215 AEs were solicited, and 43 were unsolicited. There were no adverse events of special interest, serious adverse events, or AEs leading to study discontinuation or death. All AEs were resolved by the end of the study, and no changes in treatment were necessary (***Supplemental Table 4 and 5***).

**Table 2**
Group wise vibriocidal titers against ogawa and inaba serotype at day 0 & 28 and its percent seroconversion.

| Serotype | Ogawa | | Inaba | |
|---|---|---|---|---|
| | BBV131 | Shanchol™ | BBV131 | Shanchol™ |
| Overall Total | | | | |
| N | 1345 | 449 | 1345 | 449 |
| GMT [95 % CI] at Day 0 | 33.9[30.68, 37.53] | 29.7[25.02, 35.34] | 20.7[18.78, 22.89] | 25.1[21.09, 29.96] |
| GMT [95 % CI] at Day 28 | 249.1[227.89, 272.35] | 261.3[225.32, 303.14] | 196.3[178.58, 215.86] | 194.9[168.90, 224.96] |
| $p-value at Day 0 | 0.19 | | 0.06 | |
| $p-value at Day 28 | 0.59 | | 0.93 | |
| n % seroconversion | 918 (68.25) | 305 (67.93) | 935 (69.52) | 303 (67.48) |
| ǂSCR Difference (95 % CI) | 0.0032 [−0.046, 0.054] | | 0.0203 [−0.028, 0.071] | |
| Non-inferiority criteria met | Yes | | Yes | |
| Group 1 (Age ≥ 18) 4-fold SCR | | | | |
| N | 450 | 149 | 450 | 149 |
| GMT [95 % CI] at Day 0 | 41.0[33.86, 49.72] | 34.1[24.67, 47.13] | 20.7[17.36, 24.66] | 25.1[18.48, 34.08] |
| GMT [95 % CI] at Day 28 | 270.1[235.22,310.22] | 274.2[209.68, 358.55] | 198.4[168.71,233.38] | 205.7[157.96, 267.98] |
| n % seroconversion | 311 (69.11) | 104 (69.80) | 312 (69.33) | 104 (69.80) |
| ǂSCR Difference (95 % CI) | −0.0069 [−0.088, 0.081] | | −0.0047 [−0.086, 0.084] | |
| Non-inferiority criteria met | Yes | | Yes | |
| Group 2 (Age ≥ 5 to < 18) 4-fold SCR | | | | |
| N | 447 | 150 | 447 | 150 |
| GMT [95 % CI] at Day 0 | 33.1[28.12,39.06] | 31.3[23.26, 42.09] | 21.4[18.06,25.29] | 21.6[16.23, 28.77] |
| GMT [95 % CI] at Day 28 | 261.7[221.23,309.69] | 284.8[225.36,359.94] | 201.4[171.00,237.22] | 189.0[143.76,248.49] |
| *n % seroconversion | 300 (67.11) | 100 (66.67) | 313 (70.02) | 104 (69.33) |
| ǂSCR Difference (95 % CI) | 0.0045 [−0.080, 0.094] | | 0.0069 [−0.075, 0.095] | |
| Non-inferiority criteria met | Yes | | Yes | |
| Group 3 (Age ≥ 1 to < 5) 4-fold SCR | | | | |
| N | 448 | 150 | 448 | 150 |
| GMT [95 % CI] at Day 0 | 28.7[24.34, 33.88] | 24.7[18.65, 32.63] | 20.2[16.99, 23.93] | 29.3[21.18, 40.50] |
| GMT [95 % CI] at Day 28 | 218.6[187.11,255.45] | 228.7[174.29, 299.97] | 189.4[160.13,223.99] | 190.5[154.85, 234.43] |
| *n % seroconversion | 307 (68.53) | 101 (67.33) | 310 (69.20) | 95 (63.33) |
| ǂSCR Difference (95 % CI) | 0.0119 [−0.071, 0.101] | | 0.0586 [−0.027, 0.148] | |
| Non-inferiority criteria met | Yes | | Yes | |

Data is presented as *n (%) seroconversion (4-fold) where seroconversion rates were defined by the proportion of post-vaccination titres that were at least four-fold higher than baseline. ǂSCR Difference is the difference in seroconversion rates between the two vaccine arms and Criterion for NI was two-sided 95 % CI for difference in seroconversion rates (rate for BBV131 minus rate for Shanchol™) had lower bound ≥ −10 %. The CI was calculated by a likelihood score method. % = n/N *100; n = number of subjects in the relevant population and N = Total number of subjects enrolled in the study. $Student t-test statistical analysis was used to compare GMTs of BBV131 vs Shanchol at Day 0 & Day 28.

## 4. Discussion

The results of our phase III trial of immunogenicity and safety conducted for a novel single component whole-cell inactivated oral cholera vaccine (OCV), provides substantial evidence supporting its safety and capability to induce an immune response. This pivotal trial signifies a crucial step in evaluating BBV131's performance against Shanchol™, a World Health Organization (WHO) prequalified OCV, showcasing non-inferiority and affirming the consistency in immunogenicity and safety profiles of BBV131 among a healthy Indian population of age one year and above.

In assessing the immunogenicity, the primary objective was to affirm BBV131's non-inferior effectiveness compared to the WHO-prequalified OCV Shanchol™ in eliciting vibriocidal antibody responses against *V. cholerae* serogroup O1 strains of both Inaba and Ogawa. This study investigated the vibriocidal antibody responses among participants across three age groups following the administration of two doses of BBV131 compared to Shanchol™. The results demonstrated the non-inferiority of BBV131 to Shanchol™ across all age cohorts against both the Ogawa and Inaba serotypes interms of percent vibriocidal antibody seroconversion rates (defined as an at least 4-fold titre rise in post-second dose compared to the pre-vaccination baseline level) and post-second dose geometric mean titres (GMTs) of vibriocidal titres. Seroconversion rates as well as GMTs for Ogawa and Inaba serotypes were consistent across all three manufacturing lots of BBV131, underlining the batch to batch consistency and thereby the vaccine's stable production quality. These findings aligned with previous Phase I/II study conducted in Bangladesh reinforcing BBV131's non-inferiority to Shanchol™ in inducing vibriocidal antibody responses across various age groups [17].

Interstingly, in this study, low baseline GMTs were observed across the study sites, irrespective of the status of the endemicity of *vibrio cholerae* infections. These low baseline findings are comparable with the recent clinical trial conducted in India, just prior to this trial [22]. In fact, three clinical trial sites are common in both the studies. More than 75 % of the participants, showed <320 vibriocidal tiers, and only 10–25 % of the participants showed ≥320 vibriocidal tiers indicating vaccine effectiveness (*Supplemental Table 2*). Vaccine induced response at post-vaccination in this study was also comparable with a similar GMT fold rise (*Supplemental Table 3*). However, other studies [23,24] reported higher baseline titres. Occurrence of varied baseline titres could be attributed to the differences in pre-exposure status and time of study conducted. The decline of vibriocidal titres following vaccination with killed oral cholera vaccines (OCV) has been well-documented, particularly in endemic regions like India, where antibody levels often return to baseline within a year [25,26]. This decline has raised questions about the reliability of vibriocidal titres as long-term correlates of protection against cholera. Although vibriocidal titres are shown to increase with age and correlate inversely with cholera risk in endemic areas, their role as a reliable marker of protection is less clear, particularly in young age groups [23,27].

In children, immune responses to both vaccination and natural

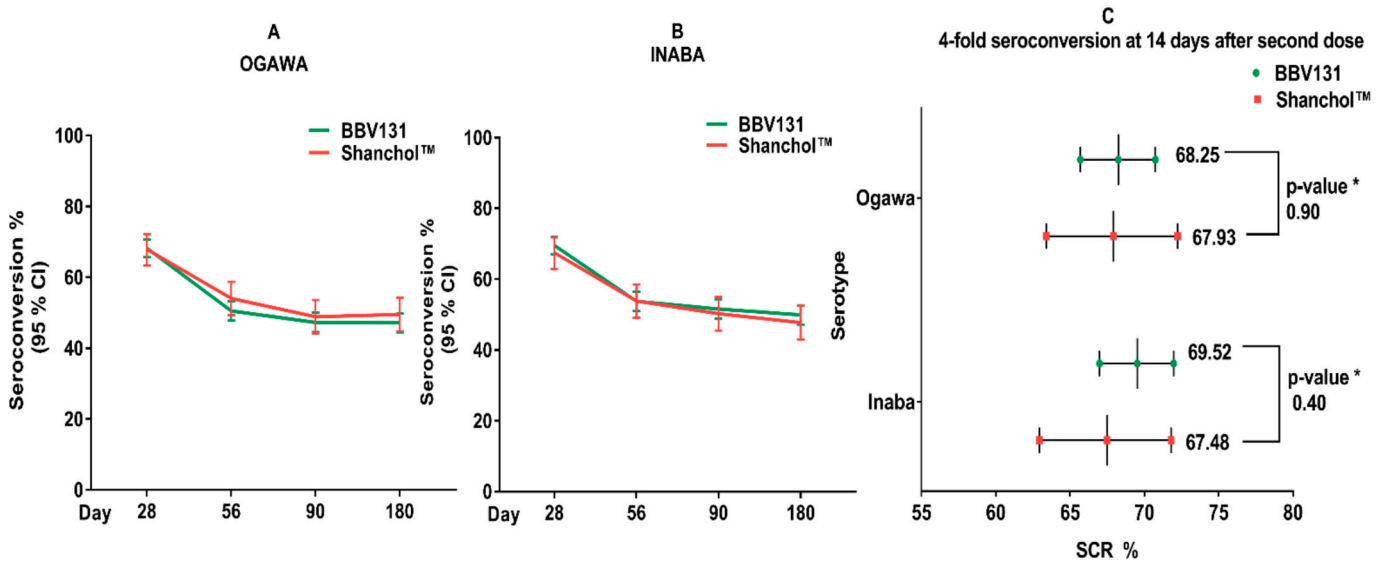


**Fig. 2.** Difference in seroconversion rate (4-fold rise from the baseline) for both ogawa and inaba serotypes.
Long-term seroconversion rates for Ogawa and Inaba of BBV131 and Shanchol™. (A). Percentage seroconversion for Ogawa of BBV131 and Shanchol™ from Day 28 to Day 180, (B). Percentage seroconversion for Inaba of BBV131 and Shanchol from Day 28 to Day 180. (C) Comparison of 4- fold seroconversion at Day 28 for Ogawa and Inaba of BBV131 and Shanchol™ *Seroconversion compared using Chi square test was used $P < 0.05$ considered statistically significant. Criterion for NI was two-sided 95 % CI for difference in seroconversion rates (rate for BBV131 minus rate for Shanchol™) had lower bound $\geq -10$ %. The CI was calculated by a likelihood score method.

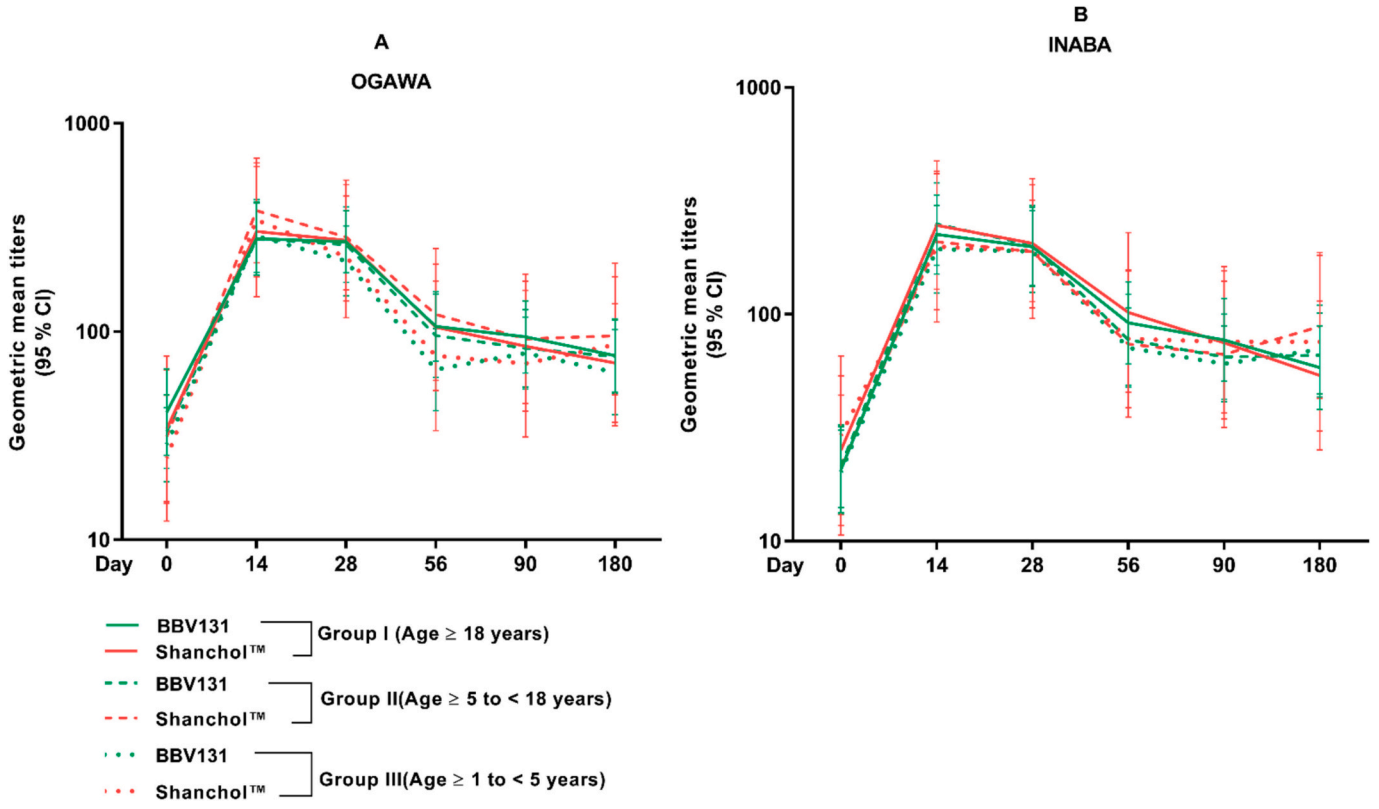


**Fig. 3.** Geometric mean titre (GMT) of anti-ogawa and anti-Inaba vibriocidal antibody titres.
GMT at Day 0 and Day 14 after 2 doses of anti Ogawa and anti Inaba of BBV131 and Shanchol™. (A) GMT for Ogawa of BBV131 and Shanchol from Day 0 to Day 180 (B). GMT for Inaba of BBV131 and Shanchol™ from Day 0 to Day 180.

infection are highly variable, leading to inconsistent protection despite elevated vibriocidal titres. This variability may be influenced by pre-existing immunity, nutritional status, and co-infections, all of which significantly impact the immune response in this vulnerable population [28]. Such findings highlight the limitations of using vibriocidal titres as a sole correlate of protection, particularly in younger individuals.

In this study, the Shanchol™ vaccine induced significant serum vibriocidal antibody responses against both Inaba and Ogawa strains 14

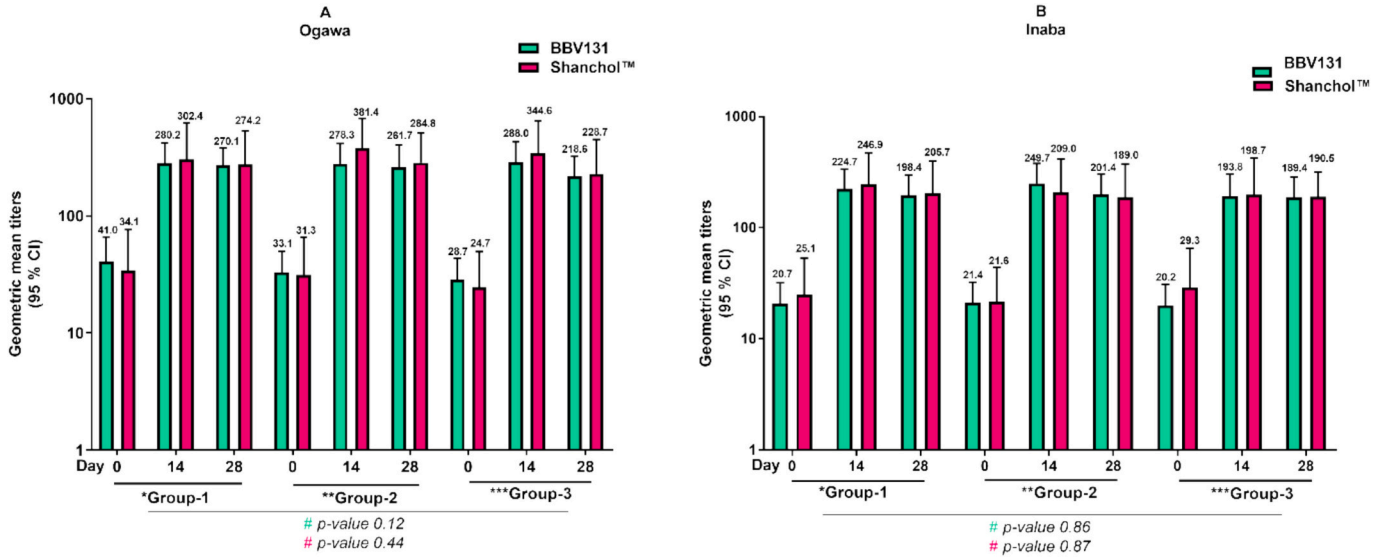


**Fig. 4.** Group-wise geometric mean titre (GMT) of anti-ogawa and anti-inaba vibriocidal antibody titres.
Group-wise GMT at Day 0 Day 14 and Day 28 after 2 doses of anti Ogawa and anti Inaba of BBV131 and Shanchol™. (A) Group-wise GMT of BBV131 and Shanchol™ at Day 0, 14 and 28 for Ogawa (B). Group-wise GMT of BBV131 and Shanchol™ at Day 0, 14 and 28 for Inaba. *Group 1: >18 years; **Group 2: > 5 < 18 years, & ***Group 3: > 1 < 5 years. # *p* value - across three groups were compared on day 28.

**Table 3**
Percent seroconversion rates of anti-ogawa and anti-inaba vibriocidal antibody titres.

| Description | BBV131 | | BBV131 | | BBV131 | |
|---|---|---|---|---|---|---|
| | Lot 1 (N = 447) | Lot 2 (N = 449) | Lot 1 (N = 447) | Lot 3 (N = 449) | Lot 2 (N = 449) | Lot 3 (N = 449) |
| Ogawa | | | | | | |
| *n (%) | 295 (66.00) | 312 (69.49) | 295 (66.00) | 311 (69.27) | 312 (69.49) | 311 (69.27) |
| ‡SCR Difference (95 % CI) | −0.0349 [−0.096, 0.026] | | −0.0327 [−0.094, 0.029] | | 0.0022 [−0.058, 0.063] | |
| Inaba | | | | | | |
| *n (%) | 319 (71.36) | 296 (65.92) | 319 (71.36) | 320 (71.27) | 296 (65.92) | 320 (71.27) |
| ‡SCR Difference (95 % CI) | 0.0544 [−0.006, 0.115] | | −0.0010 [−0.058, 0.060] | | −0.0535 [−0.114, 0.007] | |

Data is presented as *n 4-fold seroconverted subjects, (%) percent seroconversion, where seroconversion rates were defined by the proportion of post-vaccination titres that were at least four-fold higher than the baseline. ‡SCR Difference is the difference in seroconversion rates between the two lots. # 95 % CIs were calculated by a likelihood score method. % = n/N *100; n = number of 4-fold seroconverted subjects and N = Total number of subjects enrolled in the study. In the per-protocol analysis, there were a total of 5 dropouts. In Lot 1, 3 participants discontinued participation: 2 due to major deviations and 1 due to withdrawal of consent. In Lot 2 and Lot 3, there was 1 dropout each, both attributed to major protocol deviations.

days after the second dose, with levels comparable to previous findings. Although titres declined, they remained above baseline at Day 180. Similarly, earlier studies with Dukoral® have shown that vibriocidal titres often return near baseline within a year, yet these vaccines have demonstrated protective efficacy lasting up to five years post-vaccination [25].

The continued effectiveness of OCV, despite the decline in vibriocidal titres, underscores the contribution of other immune mechanisms, such as memory B cell formation, T-cell responses, and mucosal immunity [29]. Future research should focus on elucidating these broader immune responses and identifying more comprehensive correlates of protection. Hence, observational studies are especially crucial to understanding the clinical efficacy of OCV in real-world settings, particularly in young age groups, where protection mechanisms remain poorly understood [30].

Though in case of cholera, an established immune correlate of protection is not yet established, bridging studies comparing the new and existing approved vaccines can be used as a licensure approach. This bridging approach, using serum vibriocidal antibody responses, not established as an immune correlate but being specific for the targeted key protective antigen (O1 LPS), was deployed in the clinical pathway to licensure for the inactivated whole cell OCV Euvichol® (and for the later Euvichol-Plus®) being identical in composition to Shanchol™, which post approval had proven clinical efficacy in a large-scale, placebo controlled randomised clinical trial with 5 years of post-dosing follow-up. This approach, recently also leading to licensure and WHO prequalification of the 2-component Euvichol-S®, requires that the protective antigen(s) of the new and existing vaccines are defined and identical; the routes of administration of the vaccines are the same; and the vaccines are identical or similar in composition; we compared our investigational OCV with a WHO pre-qualified and safety-established vaccine Shanchol™. In view of the above, our clinical development and licensure approach has all the elements embedded for licensure and WHO pre-qualification.

Highlighting the importance of safety, the adverse events profile of BBV131 mirrored the expected outcomes associated with currently approved inactivated OCVs and was similar Shanchol™. The cumulative incidence of adverse events was observed to be almost similar in the BBV131 cohort at 13.1 % compared to 12.4 % in the Shanchol™ cohort, and no severe adverse events or particular safety concerns—such as immediate adverse events, medically attended adverse events (MAEE), adverse events of special interest or those leading to discontinuation or death—were reported. Typical solicited adverse events included symptoms such as oropharyngeal pain, dry mouth, nausea, headache, cough, and vomiting, each manifesting at a rate of less than 2 % during the first seven-day follow-up period following each vaccine dose. These findings are consistent with AE profiles delineated in earlier phase I/II study, suggesting a stable safety profile through various stages of the vaccine's development. The phase III trial results corroborate the phase I/II non-inferiority findings of Hillchol®(BBV131) versus Shanchol™ [17].

**Table 4**
Lot wise comparison of geometric mean titres (GMT) of ogawa and Inaba specific antibodies.

| Serotype | Days | GMT | | | GMT Ratio [95 % CI][#] | | |
|---|---|---|---|---|---|---|---|
| | | Lot 1 ($N$ = 447) | Lot 2 ($N$ = 449) | Lot 3 (N = 449) | Lot 1 vs Lot 2 | Lot 1 vs Lot 3 | Lot 2 vs Lot 3 |
| Ogawa | Day 0 | 36.17 | 31.43 | 34.39 | 1.151 [0.901, 1.469] | 1.052 [0.818, 1.352] | 0.914 [0.715, 1.168] |
| | Day 14 | 282.70 | 268.80 | 295.60 | 1.052 [0.837, 1.322] | 0.956 [0.765, 1.195] | 0.909 [0.721, 1.146] |
| | Day 28 | 241.80 | 257.70 | 248.10 | 0.938 [0.752, 1.170] | 0.975 [0.784, 1.213] | 1.039 [0.837, 1.290] |
| Inaba | Day 0 | 18.08 | 22.95 | 21.47 | 0.788 [0.620, 1.002] | 0.842 [0.661, 1.074] | 1.069 [0.837, 1.365] |
| | Day 14 | 227.30 | 209.00 | 228.90 | 1.087 [0.853, 1.387] | 0.993 [0.784, 1.257] | 0.913 [0.717, 1.162] |
| | Day 28 | 190.70 | 196.80 | 201.70 | 0.969 [0.766, 1.227] | 0.946 [0.752, 1.189] | 0.976 [0.774, 1.231] |

Data is presented as lot wise GMT ratio, [#]95 % CIs were calculated by a likelihood score method. Criterion for consistency of 3 lots of BBV131 is that the two-sided 95 % CI for GMT ratio of any 2 lots have lower limit ≥0.667 and an upper limit of ≤1.5. n = number of subjects. In the per-protocol analysis, there were a total of 5 dropouts. In Lot 1, 3 participants discontinued participation: 2 due to major deviations and 1 due to withdrawal of consent. In Lot 2 and Lot 3, there was 1 dropout each, both attributed to major protocol deviations.

**Table 5**
Summary of solicited adverse events during 7 days of follow-up period after overall dose.

| Primary System Organ Class Preferred Term | Group I (Age ≥ 18 years) | | Group 2 (≥ 5 to < 18 years) | | Group 3 (≥ 1 to < 5 years) | | Overall Total | | |
|---|---|---|---|---|---|---|---|---|---|
| | BBV131 (N = 450) | Shanchol™ (N = 150) | BBV131 ($N$ = 450) | Shanchol™ ($N$ = 150) | BBV131 (N = 450) | Shanchol™ (N = 150) | BBV131 ($N$ = 1350) | Shanchol™ ($N$ = 450) | Total (N = 1800) |
| | n,m (%) | n,m (%) | n,m (%) | n,m (%) | n,m (%) | n,m (%) | n,m (%) | n,m (%) | n,m (%) |
| Subjects with at least one AE | 56,59 (12.4) | 14,15 (9.3) | 50,52 (11.1) | 15,15 (10.0) | 45,46 (10.0)[1] | 16,16 (10.7) | 151,157 (11.2) [ǂ] | 45,46 (10.00) | 196,203 (10.8) [ǂ] |
| Dry mouth | 11,11 (2.4) | 3,3 (2.0) | 11,11 (2.4) | 2,2 (1.3) | 4,4 (0.9) | 2,2 (1.3) | 26,26 (1.9) | 7,7 (1.6) | 33,33 (1.8) |
| Nausea | 13,13 (2.9) | 2,2 (1.3) | 5,5 (1.1) | 3,3 (2.0) | 2,2 (0.4) | 1,1 (0.7) | 20,20 (1.5) | 6,6 (1.3) | 26,26 (1.4) |
| Vomiting | 3,3 (0.7) | 0,0 (0.0) | 8,8 (1.8) | 0,0 (0.0) | 8,8 (1.8) | 1,1 (0.7) | 19,19 (1.4) | 1,1 (0.2) | 20,20 (1.1) |
| Abdominal pain | 1,1 (0.2) | 0,0 (0.0) | 5,6 (1.1) | 0,0 (0.0) | 3,3 (0.7) | 1,1 (0.7) | 9,10 (0.7) | 1,1 (0.2) | 10,11 (0.6) |
| Mouth ulceration | 1,1 (0.2) | 0,0 (0.0) | 1,1 (0.2) | 1,1 (0.7) | 2,2 (0.4) | 2,2 (1.3) | 4,4 (0.3) | 3,3 (0.7) | 7,7 (0.4) |
| Abdominal pain | 1,1 (0.2) | 0,0 (0.0) | 1,1 (0.2) | 0,0 (0.0) | 0,0 (0.0) | 0,0 (0.0) | 2,2 (0.1) | 0,0 (0.0) | 2,2 (0.1) |
| Oropharyngeal pain | 11,11 (2.4) | 2,2 (1.3) | 6,6 (1.3) | 3,3 (2.0) | 10,10 (2.2) | 3,3 (2.0) | 27,27 (1.9) | 8,8 (1.8) | 35,35 (1.9) |
| Cough | 5,5 (1.1) | 2,2 (1.3) | 4,4 (0.9) | 2,2 (1.3) | 6,6 (1.3) | 1,1 (0.7) | 15,15 (1.1) | 5,5 (1.1) | 20,20 (1.1) |
| Headache | 7,7 (1.6) | 5,5 (3.3) | 6,6 (1.3) | 3,3 (2.0) | 0,0 (0.0) | 1,1 (0.7) | 13,13 (1.0) | 9,9 (2.0) | 22,22 (1.2) |
| Pyrexia | 3,3 (0.7) | 1,1 (0.7) | 3,3 (0.7) | 0,0 (0.0) | 3,3 (0.7) | 3,3 (2.0) | 9,9 (0.7) | 4,4 (0.9) | 13,13 (0.7) |
| Fatigue | 2,2 (0.4) | 0,0 (0.0) | 0,0 (0.0) | 0,0 (0.0) | 2,2 (0.4) | 0,0 (0.0) | 4,4 (0.3) | 0,0 (0.0) | 4,4 (0.2) |
| Decreased appetite | 0,0 (0.0) | 0,0 (0.0) | 1,1 (0.2) | 1,1 (0.7) | 6,6 (1.3) | 1,1 (0.7) | 7,7 (0.5) | 2,2 (0.4) | 9,9 (0.5) |
| Vertigo | 1,1 (0.2) | 0,0 (0.0) | 0,0 (0.0) | 0,0 (0.0) | 0,0 (0.0) | 0,0 (0.0) | 1,1 (0.1) | 0,0 (0.0) | 1,1 (0.1) |

N = number of subjects enrolled in each group, n = number of subjects, who have shown adverse events, m = count of events (one subject might have been counted more than once), % = n/N *100; [ǂ] In the study for Group III's BBV131 arm (subject 04–154), an adverse event (AE) - sore throat was erroneously recorded in the database as starting at 10:00 h instead of the actual 20:00 h on 09-Aug-2022, post the second dose of the vaccine given at 10:30 h. This error led to discrepancies in AE reporting: it was included as a solicited AE in one count ($n$ = 196, m = 203), but was incorrectly excluded in others due to appearing outside the 7-day post-vaccination window. This event should be considered solicited, following source data verification. The initial error and its subsequent correction have been meticulously documented and addressed in our data handling report to ensure the integrity of our findings.

Performing a comparative analysis against the backdrop of the phase III trial and phase I/II studies unveils consistent vibriocidal antibody responses, bolstering similar seroconversion rates and geometric mean titres for BBV131 and Shanchol™ with a participant pool of 540 across diverse age groups. This is further evidenced by a peer-reviewed comparative analysis drawing parallels between seroconversion rates of two WHO-prequalified vaccines, Euvichol Plus® and Shanchol™, within an Indian population, which aligns with the outcomes of BBV131 in the current phase III trial. Data from previous studies indicate that seroconversion rates, based on a 4-fold rise in vibriocidal assay titres, were 60 % in adults, 74 % in older children, and 84 % in toddlers among recipients of the comparator vaccine, Shanchol™ [17]. In the present Phase III trial, BBV131 is affirmed to match Shanchol™'s 70 % vibriocidal antibody seroconversion rate and post-vaccination GMTs across age groups against Ogawa and Inaba serotypes, thus reinforcing its non-inferior immunogenicity efficacy as a cholera vaccine.

Despite promising results, the study has limitations. First, the study was aim to evaluate the immunogenicity and safety did not include clinical efficacy against cholera. Second, there is no long-term immunogenicity evaluation. The observed pattern of immune response, encompassing seroconversion and alterations in vibriocidal titres, suggests a rapid decay of antibodies, mirroring results from other cholera vaccine studies. However, this decay should not be interpreted as waning immunity because immunity conferred through cholera against subsequent diseases lasts for 3–10 years [25,26]. Given these patterns, the strategic deployment of BBV131 in areas prone to outbreaks warrants consideration to accumulate real-world efficacy data.

Our study's strengths include a diverse and substantial sample size of 1800 participants across a wide age range, drawn from various locales within a cholera-endemic country. This study data significantly enhances the generalizability of the results. A meticulous evaluation of immune responses and safety profiles, coupled with the demonstration of lot-to-lot consistency, emphasizes the robustness and reliability of our findings.

The current cholera situation depicts a dire need for additional vaccine options driven by a global shortfall in OCV supply, compounded by increasing cholera incidences and serious outbreaks attributed to environmental and socio-political factors that compromise access to clean water. The cessation of Shanchol™ production by Sanofi Pasteur has exacerbated this shortage, particularly as endemic countries move to initiate prophylactic vaccination campaigns. BBV131's approval and WHO prequalification could significantly mitigate the global scarcity of oral cholera vaccines and can cater to the escalating demand.

Furthermore, BBV131 uses a single-strain, high-yield manufacturing process utilizing a formalin-inactivated engineered stable Hikojima serotype strain MS1568, positioning it as a highly efficient candidate for

**Table 6**
Summary of unsolicited adverse events.

| Primary System Organ Class<br>Preferred Term | Group I (Age ≥ 18 years) | | Group II (≥ 5 to < 18 years) | | Group III (≥ 1 to < 5 years) | | Overall Total | | |
|---|---|---|---|---|---|---|---|---|---|
| | BBV131 (N = 450)<br>n, m (%) | Shanchol™ (N = 150)<br>n, m (%) | BBV131 (N = 450)<br>n, m (%) | Shanchol™ (N = 150)<br>n, m (%) | BBV131 (N = 450)<br>n, m (%) | Shanchol™ (N = 150)<br>n, m (%) | BBV131 (N = 1350)<br>n, m (%) | Shanchol™ (N = 450)<br>n, m (%) | Total (N = 1800)<br>n, m (%) |
| Subjects with at least one AE | **8,9 (1.8 %)** | **2,2 (1.3 %)** | **19,22 (4.2 %)** | **6,6 (4.0 %)** | **8,12 (1.8 %)** | **3,3 (2.0 %)** | **35,43 (2.6 %)** | **11,11 (2.4 %)** | **46,54 (2.6 %)** |
| Pyrexia | 2,2 (0.4 %) | 2,2 (1.3 %) | 7,7 (1.6 %) | 0,0 (0.0 %) | 5,5 (1.1 %) | 3,3 (2.0 %) | 14,14 (1.0 %) | 5,5 (1.1 %) | 19,19(1.1 %) |
| Pain | 0,0 (0.0 %) | 0,0 (0.0 %) | 2,2 (0.4 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 2,2 (0.1 %) | 0,0 (0.0 %) | 2,2 (0.1 %) |
| Chills | 0,0 (0.0 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 1,1 (0.2 %) | 0,0 (0.0 %) | 1,1 (0.1 %) | 0,0 (0.0 %) | 1,1 (0.1 %) |
| Diarrhoea | 1,1 (0.2 %) | 0,0 (0.0 %) | 4,4 (0.9 %) | 2,2 (1.3 %) | 2,3 (0.4 %) | 0,0 (0.0 %) | 7,8 (0.5 %) | 2,2 (0.4 %) | 9,10 (0.5 %) |
| Gastroesophageal reflux disease | 2,2 (0.4 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 2,2 (0.1 %) | 0,0 (0.0 %) | 2,2 (0.1 %) |
| Abdominal pain upper | 0,0 (0.0 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 1,1 (0.7 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 1,1 (0.2 %) | 1,1 (0.1 %) |
| Cough | 0,0 (0.0 %) | 0,0 (0.0 %) | 2,2 (0.4 %) | 0,0 (0.0 %) | 2,2 (0.4 %) | 0,0 (0.0 %) | 4,4 (0.3 %) | 0,0 (0.0 %) | 4,4 (0.2 %) |
| Rhinorrhoea | 0,0 (0.0 %) | 0,0 (0.0 %) | 2,2 (0.4 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 2,2 (0.1 %) | 0,0 (0.0 %) | 2,2 (0.1 %) |
| Sneezing | 0,0 (0.0 %) | 0,0 (0.0 %) | 1,1 (0.2 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 1,1 (0.1 %) | 0,0 (0.0 %) | 1,1 (0.1 %) |
| Nasopharyngitis | 1,1 (0.2 %) | 0,0 (0.0 %) | 2,2 (0.4 %) | 2,2 (1.3 %) | 1,1 (0.2 %) | 0,0 (0.0 %) | 4,4 (0.3 %) | 2,2 (0.4 %) | 6,6 (0.3 %) |
| Headache | 3,3 (0.7 %) | 0,0 (0.0 %) | 1,1 (0.2 %) | 1,1 (0.7 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 4,4 (0.3 %) | 1,1 (0.2 %) | 5,5 (0.3 %) |
| Myalgia | 0,0 (0.0 %) | 0,0 (0.0 %) | 1,1 (0.2 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 0,0 (0.0 %) | 1,1 (0.1 %) | 0,0 (0.0 %) | 1,1 (0.1 %) |

N = number of subjects enrolled in each group, n = number of subjects, who have shown adverse events, m = count of events (one subject might have been counted more than once), % = n/N *100.

vaccine production and dissemination. Respule packaging using Blow fill seal technology ensures consistent high process quality, cost-effectiveness, durability, logistically viable option, and ease of administration, making it ideal for widespread distribution in cholera-endemic regions. The International Coordinating Group (ICG) on Vaccine Provision has adapted to a single-dose strategy due to the worldwide shortage of Oral Cholera Vaccines (OCV), underscoring the critical necessity for enhanced vaccine manufacturing capabilities.

Our study offers compelling evidence regarding the immunogenicity and safety of BBV131, yet it is imperative for future studies to assess its clinical efficacy in real-world settings. With the rise in cholera outbreaks, exacerbated by global warming, mass migrations, multiple global, and regional conflicts, adopting a proactive vaccination strategy is crucial. Developing thorough cholera prevention strategies, inclusive of proactive immunization efforts, is paramount for the long-term management of cholera.

In summary, BBV131 has shown comparable immunogenicity to Shanchol™ across a varied group of participants from regions endemic with cholera. Moreover, consistency across different production batches of BBV131 was confirmed, and the vaccine was generally well-received, with a positive safety profile. A notable finding is the consistent safety profiles observed during the six-month post-vaccination follow-up period and across all study age cohorts (*Supplemental Table 4 & 5*). No serious adverse events were reported, with the majority of adverse events being mild. This highlights the safety of BBV131 as a viable oral cholera vaccine option and the reliability of its manufacturing processes. The scalability and logistical benefits of BBV131 also highlight its potential to mitigate the OCV shortage. BBV131, which under trade name Hillchol® recently received market authorization in India offering more comprehensive protection against cholera.

All authors attest they meet the ICMJE criteria for authorship.

## CRediT authorship contribution statement

**Krishna Mohan Vadrevu:** Resources, Project administration, Methodology, Formal analysis, Data curation. **Abhishek Chavan:** Data curation. **Amit Chawla:** Data curation. **B.S. Chakravarthy:** Data curation. **Chandramani Singh:** Data curation. **Sagar Redkar:** Data curation. **Savita Verma:** Data curation. **Sriharsha Yandapally:** Data curation. **M. Suma Priya:** Data curation. **Vasant Khalatkar:** Data curation. **Brunda Ganneru:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation. **Siddharth Reddy:** Project administration, Data curation. **Bhargav Reddy:** Data curation. **Jan Holmgren:** Writing – review & editing. **Badri Patnaik:** Writing – review & editing, Formal analysis. **Raches Ella:** Writing – review & editing, Funding acquisition, Formal analysis, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.126998.

## Data availability

The data that has been used is confidential.

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