Immunogenicity and safety of a variant-specific COVID-19 vaccine booster, BIV1-CovIran Plus: findings from a non-inferiority, parallel-design non-randomised clinical trial

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Introduction

Newly emerging variants of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have consecutively mounted coronavirus disease-2019 (COVID-19) waves over the past two years of the pandemic. The highly contagious B.1.1.529 (Omicron) variant of concern has globally outcompeted the earlier variants during the last months with its higher rates of spike protein mutation resulting in immune evasion capability [1,2].

Disparate studies have reportedly unveiled potential escape from naturally acquired immunity of Omicron variant while challenging the effectiveness and neutralisation capacity of conventional anti-SARS-Cov-2 vaccines [1,3,4,4–6]. Although exploiting booster jabs of Wuhan-based vaccines was deemed an efficacious strategy to contain the new variant peaks, the health authorities undermined the sustainability of these mitigation strategies while underscoring the updating of vaccines originally developed against ancestral vaccines [7]. Thus, vaccine manufacturers are developing Omicron-specific booster candidates to be administered among vulnerable populations or the public [8,9].

BIV1-CovIran, an inactivated whole virus particle vaccine against SARS-CoV-2 ancestral strain, was well tolerated, with no safety concerns, and conferred 70.5% and 83.1% efficacy against hospitalisation and ICU admission, respectively, during Delta variant peak. The vaccine has reduced hospitalisation by 86.4% and deaths by 98.3% [10]. Using the previous experience in constructing the BIV1-CovIran [11] vaccine and commensurate with the global efforts in updating previous vaccines against Omicron variant, the inactivated virus platform was re-employed to develop a novel Omicron-variant-based vaccine within a month of virus isolation, titled BIV1-CovIran Plus [12].

This study reports the interim neutralisation capacity, antibody production, and safety findings from a non-randomised parallel-designed clinical trial evaluating booster shots of BIV1-CovIran Plus compared to BIV1-CovIran and BBIBP-CorV shots.

Methods

Overview

This non-randomised, non-inferiority, parallel-designed clinical trial was conducted to evaluate the non-inferiority of BIV1-CovIran Plus booster against Omicron compared with the ancestral vaccine, BIV1-CovIran, via investigating its neutralisation capacity, antibody production, and safety among 210 participants aged 18-75 years in Iran. The study protocol was reviewed and approved by National Research Ethics Committee (IR.NREC.1400.021) [13] and was registered in the Iranian Registry of Clinical Trials (IRCT20171122037571N4) [14] (Supplementary appendix 1). In this study, participants were non-randomly assigned to three arms of 70 participants to intramuscularly receive 0.5 millilitres of BIV1-CovIran or BIV1-CovIran Plus booster shot following three to five months after vaccination with BIV1-CovIran or BBIBP-CorV.

Design and Setting

The study complied with the declaration of Helsinki, good clinical practice (GCP), and the GCP of Iran as the local regulator. The study protocol, procedures, and all potential benefits/harms have been set forth to eligible volunteers and written informed consent was obtained before enrollment. An independent data safety and monitoring board (DSMB) periodically evaluated the study to ensure the safety of participants and advise the outcome assessors about the study continuation, suspension, withdrawal, and termination. The study was conducted in Tehran by administering the first vaccine dose to the first participant on 27 February 2022. The last vaccine injection of the last participant occurred on 27 March 2022. The clinical trial centre where the assessment, enrollment and vaccine administration occurred was Eram Hotel, Tehran, Iran.

Participants

Qualified volunteers aged 18 to 75 years, who had received two doses of BIV1-CovIran or BBIBP-CorV three to five months prior to enrollment, could participate in the clinical trial. Negative history of COVID-19 infection after receiving the second dose of the vaccine, negative real-time reverse transcription polymerase-chain-reaction (RT-PCR) for SARS-Cov-2 at the time of screening and the absence of suspicious symptoms for COVID-19 were mandatory to be included in the study. In addition, all volunteers must be in a stable underlying condition with no history of hospital admission three months before screening. Of note, the participants of phase I, phase II and phase III clinical trials of BIV1-CovIran were excluded from the study (Supplementary appendix 1).

Intervention and Procedure

Participants with a history of receiving two doses of BIV1-CovIran or BBIBP-CorV three to five months before enrollment were vaccinated with 0.5-millilitre vaccine doses of BIV1-CovIran Plus, containing

5μg of inactivated whole virus particle specific for the Omicron variant. Vaccine preparation, inactivation, and all procedures related to vaccine manufacturing were identical to BIV1-CovIran, and were conducted by Shifa-Pharmed Industrial Group [11,12,15]. Participants were non-randomly assigned to the either of following study arms: A) the history of BIV1-CovIran and receiving BIV1-CovIran as a booster dose; B) the history of BIV1-CovIran and receiving BIV1-CovIran Plus as booster dose; and C) the history of BBIBP-CorV and receiving BIV1-CovIran Plus as a booster dose.

Assessments

Screening, obtaining informed consent, in-person interview, and the vaccine administration were performed on day zero. Participants were closely monitored for immediate adverse reactions (ARs) within 30 minutes after injection at the clinical trial site. On day 14, after the booster dose injection, a second face-to-face follow-up visit was held, and blood samples were taken for antibody assessment. All participants could contact 24/7 call centres at the clinical trial centres should they need medical assistance or have any concerns. Suspected COVID-19 cases were defined if participants presented (1) at least two of the following symptoms lasting for at least 48 hours: fever (axillary temperature ≥37.5°C), chills, sore throat, stuffy nose, myalgia, fatigue, headache, nausea or vomiting, or diarrhoea or (2) at least one respiratory sign or symptom (including cough, shortness of breath), new olfactory or taste disorder, or radiographic evidence of COVID-19–like pneumonia. Upon the report of any suspicious COVID-19 symptoms, a nasopharyngeal specimen would be obtained at the clinical trial site, and RT-PCR would be performed at a central laboratory. In cases of negative RT-PCR tests, participants underwent further RT-PCR tests after 48 hours unless their symptoms regressed. Positive RT-PCR tests would indicate definitive symptomatic COVID-19.

Outcomes and Endpoints

The study's primary outcomes were the non-inferiority of total IgG antibodies titers against the Omicron variant 14 days after the booster dose injection in the BIV1-CovIran Plus receipients compared to the corresponding group receiving BIV1-CovIran boost (Supplementary appendix 2). In addition, evaluating the neutralisation capacity of the BIV1-CovIran Plus booster compared with the BIV1-CovIran booster using Conventional Virus Neutralisation Test (cVNT) assay was another primary outcome. The cVNT method is fully described in the study protocol (supplementary appendix 1).

Secondary outcomes included the safety profile of participants measured through adverse events (AEs), and adverse drug reactions (ADRs) described as , unsolicited, local, and systematic events.

Statistical Analysis

The safety analysis was conducted for all participants with any safety evaluation data. The incidence of AEs in each subgroup was defined as the number of participants with AEs divided by the number of

participants in the corresponding intervention/placebo subgroup. The analysis of humoral immunogenicity was conducted for all enrolled participants who had received the BIV1-CovIran/BIV1-CovIran Plus with blood collection before and 14-days after booster injection. The humoral response was assessed through geometric mean titers (GMT), and geometric mean ratios (GMR) with 95% confidence intervals (CI) of total IgG antibodies against SARS-CoV-2 Wuhan and Omicron variants using ELISA kits. The non-inferiority of study groups receiving BIV1-CovIran Plus boost to its corresponding group receiving BIV1-CovIran boost was concluded if the lower bound of 95% CI for GMR lay above of 0.67, which was based on the WHO criterion for licensing of new vaccines [16]. For cVNT, each neutralisation test was performed in triplicates. Virus-specific cytopathic effects (CPE) were visualised 72 hours later and were observed via light microscopy. Neutralising antibody titers were presented as values of the highest dilution inhibiting CPE formation.

The sample size was calculated at least 64 participants for each arm based on estimating geometric mean titer (GMT) of 10 μg/ml with a standard deviation (SD) of 3 considering test power of 90% and non-inferiority margin of 20%. The full description of the sample size calculation was provided in the study protocol (Supplementary appendix 1). Given the 10% dropout rate, 210 participants were recruited. Participants were non-randomly assigned with the ratio of 1:1:1 (70 participants with a history of BIV1-CovIran and receiving BIV1-CovIran as a booster dose; 70 participants with a history of BIV1-CovIran and receiving BIV1-CovIran Plus as booster dose; and 70 participants with the history of BBIBP-CorV and receiving BIV1-CovIran Plus as booster dose).

Frequency, mean, and standard deviation (SD) were used to describe the data. We used the Chi-Square test and Fisher's Exact test for categorised variables. D'Agostino's K-squared test to check the normality of the distribution. F-test of equality of variances was used to verify the equality of variances for the two-sample t-test. If the normality assumption was not satisfied, the means were compared using the Mann-Whitney test. In cases of normal distribution, if the variances were equal, the mean titres among groups were compared with a two-sample t-test at a two-sided 5% significance level. Otherwise, the Welch correction (Welch's t-test) was used using the two-sample t-test. The statistical analyses were conducted using R statistical packages v3.4.3 (http://www.r-project.org, RRID: SCR_001905). Data visualisations were performed using Tableau Desktop, version 2020.1, an interactive data visualisation software.

Role of the funding source

The study was supported by the Shifa-Pharmed Industrial Group (grant number 65780). The sponsor was blinded and had no role in study design, data collection, analysis, interpretation, manuscript drafting, or submission. An academic contract research organisation (CRO) affiliated with the Clinical Trial Center, Tehran University of Medical Sciences, Tehran, Iran, was in charge of clinical trial management and

monitoring. The unmasked randomisation list was not shared with the study sponsor. An independent third-party research centre (Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran) performed the data cleaning and analysis and drafted the manuscript.

Results

Characteristics of Participants

Of 316 volunteers, a total of 210 participants were recruited and non-randomly assigned to each arm (Figure 1). The mean (SD) age of participants was 39·9 (11·3) years (age range of 20-70), and 84 (40·0%) were female. The mean (SD) body mass index (BMI) of participants was 26·6 (4·2). Baseline characteristics of Trial participants are presented in Table 1.

Immunogenicity

Antibody titers

Considering the titers of total COVID-19 IgG against Wuhan, the GMT (95% confidence interval) of COVID-19 IgG on day 14 after the booster dose reached 187·89 (155·78- 226·61), 231·49 (223·34-239·95), and 209·02 (196·47- 222·37) for group 1 (BIV1-CovIran/BIV1-CovIran), 2 (BIV1-CovIran/BIV1-CovIran Plus), and 3 (BBIBP-CorV/BIV1-CovIran Plus), respectively. Simultaneously, the GMT (95% confidence interval) of total COVID-19 IgG against Omicron in corresponding groups was 191·47 (154·90-236·68), 251·14 (241·18- 261·51), and 239·00 (225·71- 253·07), respectively (Figure 3).

On day 14 after the booster, GMRs in the study population were 1·23 (1·09 to 1·39) for BIV1-CovIran/ BIV1-CovIran Plus and 1·11 (0·96 to1·29) for BBIBP-CorV/BIV1-CovIran Plus when compared with BIV1-CovIran/BIV1-CovIran, for Wuhan variant-specific total IgG. The BIV1-CovIran/BIV1-CovIran Plus group and BBIBP-CorV/BIV1-CovIran Plus showed GMRs equal to 1·31 (1·15 to 1·50) and 1·25 (1·07 to 1·45), with the lower limit of the CI above the non-inferiority margin and was statistically superior to BIV1-CovIran/BIV1-CovIran. GMTs and GMR of total IgG antibodies against Wuhan and Omicron variants are presented in Table 2.

Virus neutralisation test

Figure 2 presents the virus neutralisation titres among participants receiving BIV1-CovIran/BIV1-CovIran (group 1), BIV1-CovIran/BIV1-CovIran Plus (group 2), and BBIBP-CorV/BIV1-CovIran Plus (group 3). Considering the sera at 1/16 dilution on day zero, 23/30 (76·7%) and 2/30 (6·7%) of participants in group 1 (BIV1-CovIran/BIV1-CovIran) neutralised Wuhan and Omicron variant, respectively. On day 14, the corresponding rates were 29/30 (96·7%) and 7/30 (23·3%), respectively. Among group 2 (BIV1-CovIran/BIV1-CovIran Plus), the Wuhan variant was neutralised in 58/69 (84·6%) and 45/59 (76·3%) of participants on days 0 and 14, respectively. The rates for the Omicron variant were 32/69 (46·4%) for day zero and 39/59 (66·1%) for day 14.

In group 3 (BBIBP-CorV/BIV1-CovIran Plus), the 16-times diluted sera of 57/70 (81·4%) and 51/64 (79·7%) of participants neutralised the Wuhan variant, while 31/70 (44·3%) and 41/6 (64·0%) of participants neutralised the Omicron variant.

Safety

Among participants, the overall incidence of solicited AEs after the booster injection was 11/70 (15·7%) in group 1 (BIV1-CovIran/BIV1-CovIran), 14/70 (20·0%) in group 2 (BIV1-CovIran/BIV1-CovIran Plus), and 12/70 (17·1%) in group 3 (BBIBP-CorV/BIV1-CovIran Plus). Among all three groups of participants, the most prevalent AE was pain at the injection site (Table 3). All AEs among the vaccinated participants were mild or moderate. In addition, the follow-up of the second week after the injection showed that none of the possible AEs were severe and required therapeutic intervention. During the follow-up, a 28-year-old man complained of coughing eight days after a booster shot and tested positive for SARS-Cov-2.

Discussion

This study presents the findings from a non-randomised, parallel-designed clinical trial evaluating the non-inferiority of an inactivated whole virus particle variant-specific COVID-19 vaccine booster against SARS-CoV-2 Omicron variant, BIV1-CovIran Plus, compared with the ancestral vaccine, BIV1-CovIran, via investigating its neutralisation capacity, antibody production, and safety among participants aged 18-75 years, previously immunised with two doses of BIV1-CovIran [11,15] or BBIBP-CorV [17], which are inactivated whole virus particle vaccines developed against SARS-CoV-2.

During the study, the BIV1-CovIran Plus booster was well-tolerated among the recipients, and no serious adverse events occurred. The most common adverse event in the study was a pain in the injection site. BIV1-CovIran [15], BIV1-CovIran Plus [12], and BBIBP-CorV [18] all contained aluminium hydroxide adjuvant, which could commonly result in pain in the injection site and tenderness.

A 5µg booster dose of BIV1-CovIran Plus induced superior Omicron-specific total IgG antibody two weeks after administration compared to the original BIV1-CovIran or BBIBP-CorV vaccines. Less than 25% of the 16-fold diluted sera of participants who received the ancestral vaccine as a booster neutralised the Omicron variant; however, this figure surpassed 66% among participants who received the Omicron-specific booster. In the meantime, the Omicron-specific vaccine also retained the neutralisation activity against the Wuhan strain. Thus, this vaccine candidate could also be used against the ancestral strain.

The distinction in the rise of the omicron-specific total IgG was not as significant as expected among the participants who received the conventional vaccine compared with the Omicron-specific vaccine. Nevertheless, the results were not compatibly backed-up by cVNT, as the sera of BIV1-CovIran Plus recipients were much more potent in neutralising the Omicron variant. This could suggest that the proportion of functional neutralising antibodies against Omicron was higher among recipients of the Omicron-specific vaccine. While booster vaccination with the conventional COVID-19 vaccines tends to promote IgG and neutralising antibody concentrations [19], cross-reactive antibodies are less likely to retain functionality against the Omicron variant [20].

Although vaccination against COVID-19 has averted tens of millions of deaths globally [21], the effectiveness of primary vaccination has waned over time against the Omicron variant. Considering the waning effectiveness of the first booster doses of the vaccines initially developed against the Wuhan variant, it is critical to develop safe and effective vaccine boosters which could induce effective immunity against circulating and emerging variants of SARS-CoV-2 [22]. Thus, vaccine manufacturers began developing Omicron-specific vaccine candidates since the identification of Omicron in November 2021, the interim results of which are being published [9,23].

Strengths and limitations

Based on the follow-up data, the BIV1-CovIran Plus booster was safe and induced immunity against the SARS-CoV-2 Omicron variant. Moreover, the induced immunity against the Wuhan strain was non-inferior to BIV1-CovIran and BBIBP-CorV. The whole virus inactivation, validation, purification, and formulation of BIV1-CovIran Plus was done in a month-length timeline [12]. The trial was initiated immediately after the Omicron-specific vaccine production, indicating the capacity to rapidly respond to new circulating variants of concern. The booster of BIV1-CovIran Plus was compared with two other inactivated whole virus particle vaccines, developed initially against the Wuhan strain of SARS-CoV-2: BIV1-CovIran, which was the conventional vaccine, and BBIBP-CorV, which has been the most widely used COVID-19 vaccine in Iran [10]. The limitations of this study included its non-randomised design and small sample size. This study presents the results of a two-week follow-up after a booster administration by BIV1-CovIran Plus. Thus, the occurrence of AEs beyond the study period needs to be determined in future studies. Moreover, as vaccine-induced immunity tends to wane over time, it is pivotal to study the persistence of potentially protective immune responses. This study assessed the antibody response by determining the geometric mean titres of total IgG induced against the Wuhan and Omicron strains. While it was planned to investigate the induced humoral immunity based on anti-spike protein, anti-RBD, and neutralising antibody, the ELISA kits developed against the Omicron variant were not commercially available at the time of the study. Thus, total IgG against Wuhan and Omicron strains were investigated and compared in the study (Supplementary appendix 2). A conventional virus neutralisation test [24] was performed to evaluate the levels of functional antibodies raised against both strains. Nevertheless, cellular immunity induced by vaccination was not assessed in the study. Moreover, longer follow-up periods are required to characterise the antibody persistence and to investigate the vaccine effectiveness.

Conclusions

A 5µg booster dose of BIV1-CovIran Plus was well-tolerated and induced a superior neutralising antibody response against the Omicron variant two weeks after administration compared to the original BIV1-CovIran or BBIBP-CorV vaccines. Thus, this study presents promising results for this Omicron-specific vaccine to be used as a booster.

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Ethical statement

Ethical approval

The study protocol was approved by the National Research Ethics Committee under the reference code of IR.NREC.1400.021, and was registered at the Iranian Registry of Clinical Trials (IRCT20171122037571N4).

Data availability statement

De-identified, individual participant data will be made available when the trial is complete, upon requests directed to the corresponding author; after the approval of a proposal, data can be shared through a secure online platform.

Contributors

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Payam Tabarsi was the principal investigator of another SARS-CoV-2 vaccine trial. Hamed Hosseini was the manager of the Clinical Trial Center (CTC), an academic CRO affiliated with the Tehran University of Medical Sciences, and he was responsible for the conduct and monitoring of clinical trials. He was also a non-voting member of DSMB, which was mandated by national regulations. As the

principal investigator, Minoo Mohraz received funding for project administration from Shifa-Pharmed Industrial Group (grant number 65780). Asghar Abdoli is the founder and the scientific director of Amirabad Virology Lab and the only shareholder of this laboratory. He was also a project consultant for another SARS-CoV-2 vaccine trial. All other co-authors declare no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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343 **Tables**

Table 1. Baseline characteristics of participants

Study population	Group 1* (n= 70)	Group 2** (n= 70)	Group 3*** (n= 70)
Age (years), mean (SD)	41·3 (12·3)	36·1 (10·6)	42·3 (9·9)
Sex, n (%)			
Female	38 (54·3)	22 (31·4)	24 (34·3)
Male	32 (45·7)	48 (68·6)	46 (65·7)
Height (cm), mean (SD)	167·9 (9·4)	172·1 (10·6)	170·5 (9·6)
Weight (kg), mean (SD)	73·9 (14·0)	77·4 (19·2)	79·8 (14·1)
BMI, mean (SD)	26·1 (3·9)	26·0 (5·1)	27·5 (4·4)
Comorbidity, n (%)			
Hypertension	0 (0·0%)	4 (5·7)	10 (14·3)
Diabetes Mellitus	2 (2·9)	1 (1·4)	4 (5·7)
Hypothyroidism	1 (1·4)	3 (4·3)	1 (1·4)

*Group 1 received two doses of BIV1-CovIran and BIV1-CovIran for the booster dose.
**Group 2 received two doses of BIV1-CovIran and BIV1-CovIran Plus for the booster dose.
***Group 3 received two doses of BBIBP-CorV and BIV1-CovIran Plus for the booster dose.

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Table 2. Geometeric mean titres and Geometric mean ratios (95% confidence intervals) of antibodies at day 0 and day 14 post-booster injection

Antibody	Geometric mean titre (μg/ml) (95% CI)			Geometric mean ratio[#] (95% CI)	
	Group 1[*]	Group 2[*]	Group 3[***]	Group 2	Group 3
COVID-IgG (Wuhan)					
Time 0	113·05 (101·37, 126·07)	122·8 (110·01, 137·08)	132·49 (121·68, 144·25)	1·09 (0·93, 1·27)	1·17 (1·02, 1·34)
Time 14	187·89 (155·78, 226·61)	231·49 (223·34, 239·95)	209·02 (196·47, 222·37)	1·23 (1·09, 1·39)	1·11 (0·96, 1·29)
COVID-IgG (Omicron)					
Time 0	123·78 (113·5, 135)	129·2 (115·62, 144·39)	143·26 (131·9, 155·6)	1·04 (0·91, 1·2)	1·16 (1·03, 1·3)
Time 14	191·47 (154·9, 236·68)	251·14 (241·18, 261·51)	239 (225·71, 253·07)	1·31 (1·15, 1·5)	1·25 (1·07, 1·45)

[#] non-inferiority margin is 0·67.
[*]Group 1 received two doses of BIV1-CovIran and BIV1-CovIran for the booster dose.
[**]Group 2 received two doses of BIV1-CovIran and BIV1-CovIran Plus for the booster dose.
[***]Group 3 received two doses of BBIBP-CorV and BIV1-CovIran Plus for the booster dose.

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Table 3. Solicited and unsolicited adverse events among participants

System Organ Classification	Event	Solicited Adverse Events (0-7 days)			Unsolicited Adverse events (8-14 days)		
		Group 1*	Group 2**	Group 3***	Group 1	Group 2	Group 3
Injection Site Reaction	Pain	4	5	3	0	1	0
	Induration/Swelling	0	0	0	0	0	0
	Erythema/Redness	1	0	1	0	0	0
Gastro0intestinal system disorders	Abdominal Pain	0	1	0	0	0	0
	Vomiting	0	0	0	0	0	0
	Diarrhea	0	0	0	0	0	0
	Nausea	1	0	1	0	0	0
Respiratory system disorders	Sore Throat	0	2	0	0	0	0
	Rhinitis	0	1	0	0	0	0
	Coughing	0	0	1	0	1	0
	Dysphonia	0	0	0	0	0	0
	Epistaxis	0	0	0	0	0	0
Skin and appendages disorders	Acne	0	0	0	0	0	0
	Pruritus	0	0	0	0	0	0
	Sweating Increased	1	0	0	0	0	0
Body as a whole0general disorders	Fever	0	1	0	0	0	0
	Fatigue	1	0	1	0	0	1
	Rigors	0	1	0	0	0	0
	Asthenia	0	0	0	0	0	0
Central & peripheral nervous system disorders	Vertigo	1	0	0	0	0	0
	Headache	0	1	2	0	1	0
Cardiovascular disorders0general	Hypotension	0	0	0	0	0	0
	Palpitation	0	0	1	0	0	0
Vascular (extracardiac) disorders	Flushing	1	0	0	0	0	0
Musculo0skeletal system disorders	Myalgia	1	2	2	0	0	0

*Group 1 received two doses of BIV1-CovIran and BIV1-CovIran for the booster dose.
**Group 2 received two doses of BIV1-CovIran and BIV1-CovIran Plus for the booster dose.
***Group 3 received two doses of BBIBP-CorV and BIV1-CovIran Plus for the booster dose.

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Figures

Figure 1. The flowchart of the clinical trial.

Figure 2. The virus neutralisation titres among the study groups in conventional virus neutralisation test (cVNT) on days 0 and 14 for the Omicron (A) and the Wuhan (B) variants of SARS-CoV-2. Group 1-first and second doses: BIV1-CovIran, booster: BIV1-CovIran. Group 2-first and second doses: BIV1-CovIran, booster: BIV1-CovIran Plus. Group 3-first and second doses: BBIBP-CorV, booster: BIV1-CovIran Plus.

Figure 3. Anti-SARS-CoV-2 total IgG antibody titres against Omicron (A) and Wuhan (B). Box plots present the second quartile in dark red and the third quartile in pale red.