Efficacy and safety of an inactivated virus-particle vaccine for SARS-CoV-2, BIV1-CovIran: randomised, placebo controlled, double blind, multicentre, phase 3 clinical trial

Minoo Mohraz,[1] Katayoun Vahdat,[2] Seyyed-Hadi Ghamari,[3] Mohsen Abbasi-Kangevari,[3] Erfan Ghasemi,[3] Yasaman Ghabdian,[4] Negar Rezaei,[3,5] Maryam Amini Pouya,[6] Asghar Abdoli,[7,8] Mohammad-Reza Malekpour,[3] Keyvan Koohgir,[9] Sahar Saeedi Moghaddam,[3] Payam Tabarsi,[10] Mohsen Moghadami,[11] Farzin Khorvash,[12] Rozita Khodashahi,[13] Mohammadreza Salehi,[14] Hamed Hosseini[15,16]

For numbered affiliations see end of the article

Correspondence to: M Salehi mr-salehi@sina.tums.ac.ir (ORCID 0000-0002-5538-7586)

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ABSTRACT

OBJECTIVE

To report the efficacy, safety, and exploratory immunogenicity findings of two 5 µg doses of the BIV1-CovIran vaccine.

DESIGN

Randomised, placebo controlled, double blind, multicentre, phase 3 clinical trial.

SETTING

In six cities of Iran, including Bushehr, Isfahan, Karaj, Mashhad, Shiraz, and Tehran. The first vaccine or placebo injection of the first participant was on 16 May 2021 in Tehran. The last vaccine or placebo injection of the last participant occurred on 15 July 2021 in Isfahan.

PARTICIPANTS

20 000 participants aged 18-75 years were randomly assigned to the intervention/placebo groups with a ratio of 2:1.

INTERVENTION

5 µg vaccine or placebo with the interval of 28 days.

MAIN OUTCOME MEASURES

The vaccine efficacy for a 90 day follow-up period; safety, and explanatory immunogenicity assessment; and variant detection during the trial.

RESULTS

20 000 participants were recruited and randomly assigned to receive BIV1-CovIran (n=13 335 (66.7%)) or placebo (n=6665 (33.3%)). Participants' mean age was 38.3 (standard deviation 11.2) years, and 6913 (34.6%) were female. Among vaccinated participants that had covid-19 reported during the follow-up (median 83 days), 758 (5.9%) had symptoms, 144 (1.1%) had severe infection, and seven (0.1%) were critical. Among participants who received placebo during the follow-up, 688 (10.7%) had symptoms, 221 (3.4%) had severe infection, and 19 (0.3%) were critical. Overall efficacy was 50.2% (95% confidence interval 44.7% to 55.0%) against symptomatic covid-19, 70.5% (63.7% to 76.1%) against severe disease, and 83.1% (61.2% to 93.5%) against critical cases. Two deaths were reported in the efficacy population in the placebo group, no deaths were from the intervention group. During follow-up, 41 922 adverse events were reported: 28 782 (68.7%) were adverse reactions, of which 19 363 (67.3%) were in the intervention group. Most adverse reactions were mild or moderate in severity (grade 1 or 2) and self-limiting. No serious adverse events were related to the injections. For variant investigation, of 119 participants positive for the SARS-CoV-2 variant, 106 (89.1%) were positive for the delta variant.

CONCLUSIONS

A two dose regimen of the BIV1-CovIran vaccine conferred efficacy of 50.2% against symptomatic covid-19, 70.5% against severe disease, and 83.1% against critical disease. Vaccination was well tolerated, with no safety concerns raised.

TRIAL REGISTRATION

Iranian Registry of Clinical Trials, IRCT20201202049567N3.

FUNDING

Shifa-Pharmed Industrial Group.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Iran developed an inactivated whole virus particle vaccine for SARS-CoV-2, BIV1-CovIran; in-vivo immunogenicity and the protection of the BIV1-CovIran vaccine have been recently reported

The phase 1 and phase 2 clinical trials of the BIV1-CovIran showed a potentially safe and immunogenic vaccine candidate

The efficacy of this vaccine against symptomatic, severe, critical covid-19 disease, and deaths due to covid-19 infection, has not been previously investigated

WHAT THIS STUDY ADDS

Preliminary results are reported for 20 000 participants in six cities of Iran assessing two injections of BIV1-CovIran at 28 day intervals against symptomatic, severe, and critical cases and death

At 90 days, vaccine efficacy was 70.5% (95% confidence interval 63.7% to 76.1%) against severe covid-19 infection and 83.1% (61.2% to 93.5%) against critical cases; protection against related death was 100%

Preliminary vaccine efficacy against symptomatic covid-19 infection was 50.2% (44.7% to 55.0%); with a vaccine efficacy of 90.7% (81.0% to 96.0%) among participants aged 65-75 years

Introduction

The covid-19 pandemic has officially led to more than 5.6 million deaths globally.[1] Given the pandemic's medical, economic, and social consequences, the production of effective and safe vaccines against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is considered a potential pathway for controlling the crisis.[2] Several covid-19 vaccines have shown promising

results in phase 3 clinical trials so far, and vaccinations began in early 2021.[3 4] World Health Organization (WHO) has authorised emergency use for six vaccines and continues to evaluate additional proposals.[5] Nevertheless, the SARS-CoV-2 delta (B.1.617.2) variant, first detected in England in March 2021, rapidly became the predominant lineage due to its high transmissibility. Quickly, the delta variant resulted in a higher emergency care attendance or hospital admission risk than the previous variants.[6] Moreover, evidence suggests that the effectiveness of some covid-19 vaccines against the delta variant could be lower than the alpha variant, especially after a single vaccine dose.[7]

We previously reported phase 1 and phase 2 safety and immunogenicity results from clinical trials of the BIV1-CovIran vaccine,[8] an inactivated whole virus particle vaccine.[9] Following the administration of the two injections of 5 µg BIV1-CovIran vaccine at a 28 day interval, no severe adverse events related to the vaccine were reported. Moreover, the vaccine significantly enhanced the immunity of all vaccine recipients against SARS-CoV-2. In phase 2, the seroconversion rate of the neutralising-antibody was 82.8% two weeks after the second dose.[8] These findings supported the progression of the BIV1-CovIran vaccine into phase 3.

We report efficacy, safety, and exploratory immunogenicity findings from a multicentre randomised, placebo-controlled, phase 3 clinical trial evaluating two 5 µg injections of BIV1-CovIran vaccine with a 28 day interval and a 90 day follow-up following 14 days after the second injection, with the participation of 20 000 individuals aged 18-75 years. Given that the delta variant was initially reported in Iran on 8 June 2021,[10] which overlapped with this phase 3 clinical trial, the results could also shed light on the vaccine efficacy of this variant.

Methods

Overview

This randomised, placebo-controlled, double blind, multicentre, phase 3 clinical trial was conducted to further investigate the efficacy (90 day follow-up) and safety of an inactivated whole virus particle vaccine, BIV1-CovIran, among 20 000 participants aged 18-75 years from six cities of Iran. We also aimed to perform an explanatory immunogenicity assessment from a sample of 400 participants. The study protocol was approved by the National Research Ethics Committee under the reference code of IR.NREC.1399.008, was registered at the Iranian Registry of Clinical Trials (IRCT20201202049567N3) and is presented in the supplementary appendix 1. In this study, participants were randomly assigned to receive two intramuscular doses of the BIV1-CovIran vaccine with a 28 day interval. The vaccine's dosage selection, safety, and immunogenicity were evaluated in the phase 1 and phase 2 clinical trials.[8]

Table 1 | Timeline of phase 3 clinical trial in each city in 2021

	First injection		Second injection	
City	Start day	End day	Start day	End day
Tehran	16 May	31 May	13 June	28 June
Mashhad	10 June	17 June	08 July	15 July
Isfahan	10 June	17 June	08 July	15 July
Shiraz	09 June	16 June	07 July	14 July
Karaj	26 May	05 June	23 June	03 July
Bushehr	09 June	16 June	07 July	15 July

Study design

The study abided by the declaration of Helsinki, good clinical practice, and the good clinical practice of Iran as the local regulator. All eligible volunteers were precisely and thoroughly delineated about the study protocol and procedures, and written informed consent was obtained before enrolment. The data safety and monitoring board independently supervised the study and assisted the outcome assessors regarding the study continuation, suspension, withdrawal, and termination. All participants, outcome assessors, data managers, statisticians, and other study related personnel were unaware of the group allocations.

The study was conducted in six cities of Iran (ie, Bushehr, Isfahan, Karaj, Mashhad, Shiraz, and Tehran) in predetermined vaccination centres. The first vaccine or placebo dose of the first participant was administered on 16 May 2021 in Tehran. The last vaccine or placebo injection of the last participant occurred on 15 July 2021 in Isfahan. The detailed scheduling for phase 3 in each city is presented in table 1. Figure 1 presents the mapping of the timeline of the phase 3 clinical trial with the time trend of covid-19 weekly new cases and mortality in Iran.

Study participants

Invitations to participate were broadly shared on mass and social media platforms. Eligible volunteers were reached by phone calls from study physicians and then received detailed explanations about the study protocol and procedures. Willing and eligible volunteers were invited to an in-person appointment at a determined time and date. In a pre-enrolment session, the participants were briefed about the procedures. Then, the volunteers provided written informed consent and underwent a screening evaluation, including medical history documentation, physical examination, and laboratory assessments. Negative real-time reverse transcription polymerase chain reaction (RT-PCR) was obligatory to be included in the study (supplementary appendix 1).

Sample size

A total of 20 000 participants (with a ratio of 2:1 between intervention to placebo) were included in the study. The covid-19 incidence rate was estimated to be 1% per month among the population in Iran who were not immunised. We assumed that participants in each study group would have a 10% dropout rate during the trial. Thus, with a 60% expected ultimate efficacy of the vaccine, a total of 108 cases of covid-19 (48 cases in the intervention and 60 in the placebo group) were expected. At the time of the study design, we considered that 150 cases of covid-19 across the vaccine and placebo groups would yield the WHO

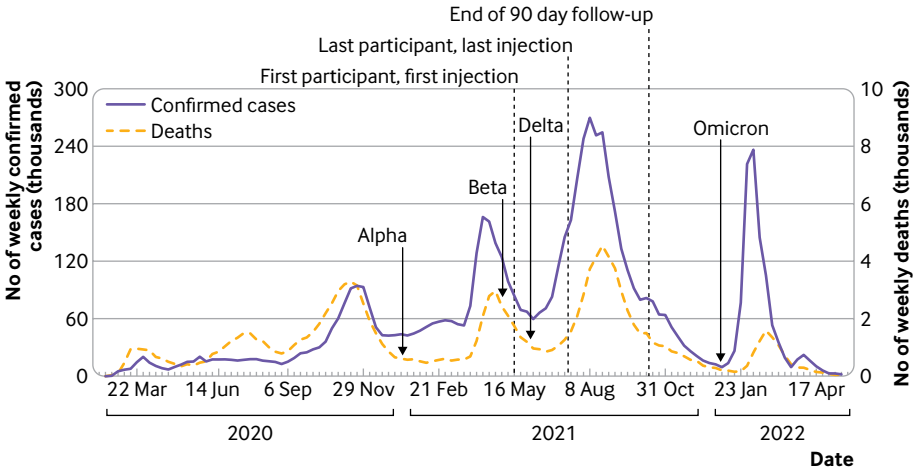


Fig 1 | Mapping the timeline of phase 3 clinical trial with the time trend of covid-19 weekly new cases and mortality in Iran by mid-May 2022

recommendation of ultimate efficacy of 60% (lower bound of 30%). The number of participants in each city was cardinally determined commensurate with the city population, where each trial site was located. To match the study population's age distribution to the age pyramid of the country,[11] 20% of the study population in each city included participants aged 51-75 years. Participants were randomly assigned to the intervention or placebo groups (2:1) within each city.

Randomisation and enrolment

We used an electronic tool[12] to produce the randomisation sheet subsuming block sequences of three and six. A unique four-character randomisation code was generated on enrolment of each eligible participant using the electronic tool.[12] Then, four other letters were added to the randomisation code: the first two letters of the participant's first name and the first two letters of their last name to form the participant's unique code. During the trial, all procedures were performed using the participant's unique code, and the identification information remained confidential by the principal investigator.

Concealment and masking

Vaccine and placebo vials were manufactured with the same appearance, label, and participant unique code, to ensure the masking of participants, researchers, and outcome assessors. After the vaccine or placebo administration, the participant's unique code and administration date were written on the outer packaging box and the label was recorded on the randomisation sheet. The study personnel checked all the information before the vaccine or placebo administration. During the study, all packages were archived and maintained. In cases of any emergency events, including serious adverse events, the principal investigator would ask for emergency decoding and unblinding.

Intervention and procedure

All participants in the intervention group received two injections of 0.5 mL doses of 5 µg inactivated whole virus particle vaccine, BIV1-CovIran, manufactured by Shifa-Pharmed Industrial Group with an interval of 28 days. The SARS-CoV-2 virus used in vaccine production was isolated from the nasopharyngeal specimen of an Iranian patient with covid-19 and had a 99.9% identity to the earliest detected strain, Wuhan Hu-1.[13] The vaccine was inactivated with β-propiolactone and adjuvanted with Alhydrogel. The virus was sequenced and cultured using a Vero cell manufacturing platform in a biosafety level 3 facility. Participants in the placebo group received an identical solution containing the same aluminium-hydroxide adjuvant. Vaccine and placebo vials were similar in size, shape, and colour and were stored at 2-8°C. After receiving the first dosage, individuals who experienced a temperature over 39°C for more than three consecutive days or any severe allergic reaction and serious adverse events would not proceed to receive the second dose. In addition, participants with positive RT-PCR following the first administration were excluded from the second injection.

Assessments

Participants were monitored for 30 min after injection for immediate adverse events. In phase 3, participants underwent face-to-face interviews during the screening session, first injection day, and second injection day. Additionally, follow-ups by telephone were held on a 14 day interval following the injection. A reactogenicity diary book was allocated to participants regarding any possible covid-19 symptoms. All phase 3 participants would contact 24/7 study call centres, providing video call or file sharing features, should they have any concerns or need medical attention using a mobile application designed for this clinical trial. Suspected covid-19 cases were defined if participants presented at least two of these symptoms lasting for at least 48 h: fever (axillary temperature ≥37.5°C), chills, sore throat, stuffy nose, myalgia, fatigue, headache, nausea or vomiting, or diarrhoea; or at least one respiratory sign or symptom (eg, cough or shortness of breath), new olfactory or taste disorder, or radiographical evidence of covid-19-like pneumonia. On the report of any

suspicious covid-19 symptoms, a nasopharyngeal specimen was obtained at the clinical trial site, and RT-PCR was done 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. Covid-19 severity status was categorised as symptomatic, severe, and critical, based on the diagnosis scheme from the WHO (supplementary appendix 1).[14]

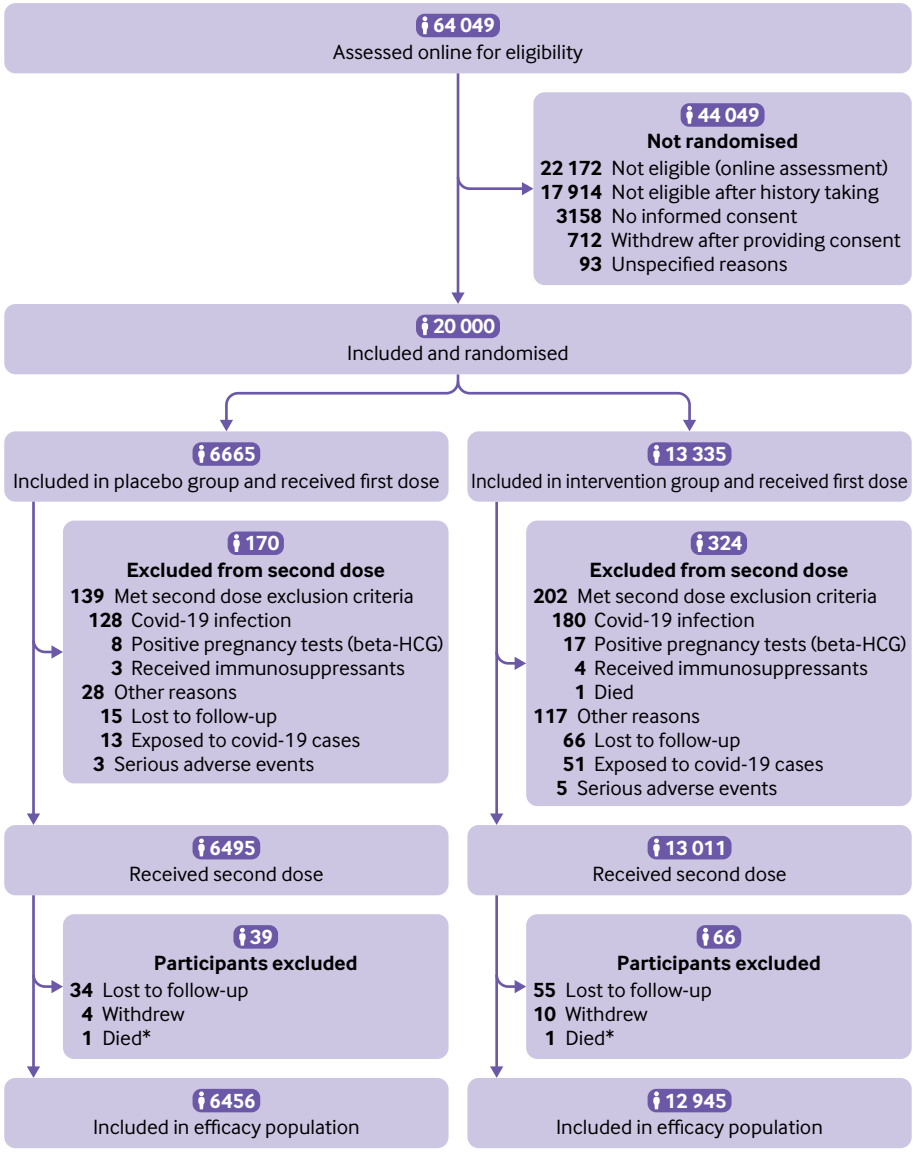
Study endpoints

Efficacy endpoints

The efficacy of BIV1-CovIran was primarily assessed by the onset of definitive symptomatic covid-19 infection during a 90 day follow-up following 14 days after the second injection. Participants received two doses of the vaccine candidate on days zero and 28. The follow-up of participants began 14 days after the second dose (day 42) to day 132 (90-day follow-up period). The onset of severe and critical covid-19 among participants of phase 3 and deaths due to covid-19 during the 90 day follow-up were assessed as the secondary efficacy endpoints. Additionally, we evaluated the post hoc efficacy of the BIV1-CovIran vaccine for covid-19 symptomatic cases, admissions, and death by subgroups, including sex, age, serology, and location.

Safety endpoints

Immediate adverse events were assessed by monitoring participants 30 min after injection in the trial centre. All participants were required to report all local and systematic adverse reactions and adverse events after the injection using the trial's mobile application. Solicited adverse reactions were defined as any events that occurred from day zero to day seven after each injection. Unsolicited adverse reactions were defined



*Death occurred within 14 days after second injection; thus, not included in efficacy population

Fig 2 | Diagram of screening, enrolment, randomisation, and follow-up in phase 3

as any adverse reactions which occurred from day eight to day 28 after each injection. The severity of adverse reactions was defined using the Food and Drug Administration guidance for industry and toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials.[15]

Exploratory immunogenicity endpoints

To further evaluate the immunogenicity enhancement of the BIV1-CovIran vaccine among phase 3 participants, the humoral response against SARS-CoV-2 in a subsample of 400 participants in Tehran was assessed by use of the convenience sampling method. The first 400 participants from the Tehran location were chosen to be assessed for exploratory immunogenicity response. The participants provided a separate informed consent for this procedure. We evaluated the geometric mean titres, geometric mean ratios of antibodies against SARS-CoV-2, and the seroconversion rates 14 days after the second injection. The blood samples were collected from the participants before the first injection and on day 14 after the second injection. Neutralising, anti-receptor binding domain, and anti-spike glycoprotein antibodies were measured using enzyme linked immunosorbent assay (known as ELISA) kits.[8] Seroconversion was defined as a postvaccination IgG titre that was at least fourfold higher than the baseline titre.

Dominant variant

Between 8 August 2021 to 13 October 2021, a subsample of symptomatic phase 3 participants from the Tehran trial site was selected via convenience sampling method for investigating the dominant variant during the trial.

Statistical analysis

Vaccine efficacy was calculated using a Poisson regression compared to the placebo group, defining the dependent variable as the number of incident cases, the independent variable as the treatment group, and the offset as the person-years. Efficacy was analysed by use of the efficacy population, who were fully vaccinated and had a vaccine or placebo administration interval of 28 days (standard deviation 3). Efficacy was assessed by the onset of covid-19 among the efficacy population who were followed for 90 days following 14 days after the second dose. The maximum contribution of each participant to person-time equalled 0.246 (90/365) person-years. Simultaneously, the vaccine efficacy against severe and critical cases of covid-19 and deaths due to covid-19 was analysed. In this phase 3 trial, the study population was assumed that missing covariates at baseline would not significantly affect the vaccine efficacy calculation and were not imputed.

Vaccine efficacy (%) = (1−incidence density of intervention group/incidence density of placebo group) × 100

Incidence density = (no. of confirmed cases during the effective follow-up/no. of observation years of all vaccinated participants) × 100.

Additionally, we did an exploratory post hoc analysis to assess the subclass group vaccine efficacy analysis based on study sites, sex, age groups, and baseline serology (IgG or IgM) status. Interaction testing

Table 2 | Baseline characteristics of participants among participants aged 18-75 years

Study population	Intervention group (n=13 335)	Placebo group (n=6665)
Age (years), mean (SD)	38.3 (11.2)	38.2 (11.1)
Age groups, n (%):		
18-50 years	11 035 (82.8)	5,564 (83.5)
51-75 years	2300 (17.2)	1101 (16.5)
Sex, n (%):		
Female	4606 (34.5)	2307 (34.6)
Male	8729 (65.5)	4358 (65.4)
Study site, n (%):		
Tehran	5812 (43.6)	2904 (43.6)
Mashhad	1911 (14.3)	956 (14.3)
Isfahan	1781 (13.4)	890 (13.4)
Shiraz	1552 (11.6)	776 (11.6)
Karaj	1324 (9.9)	661 (9.9)
Bushehr	955 (7.2)	478 (7.2)
Height (cm), mean (SD)	172.0 (9.5)	171.9 (9.5)
Weight (kg), mean (SD)	78.9 (16.1)	78.6 (16.1)
Body mass index, mean (SD)	26.5 (4.5)	26.5 (4.5)
Comorbidity, n (%):		
Cardiovascular disease	728 (5.5)	367 (5.5)
Diabetes and other endocrinology disease	310 (2.3)	173 (2.6)
Liver and gastrointestinal	27 (0.2)	17 (0.3)
Respiratory disease	13 (0.1)	6 (0.1)
Other	99 (0.7)	28 (0.4)
None	12 403 (93.0)	6169 (92.6)
Positive baseline IgG antibody, n (%)	2825 (21.2)	1488 (22.3)
Positive baseline IgM antibody, n (%)	1480 (11.1)	665 (10.0)

SD=standard deviation.

Table 3 | Efficacy of BIV1-CovIran vaccine for various covid-19 outcomes

Outcome	Intervention (n=12 945)	Placebo (n=6456)
Person-years	3126.8	1414.8
Symptomatic covid-19 infection:		
Number of incident cases	758	688
Incidence density per 1000 person-years, (95% CI)	242.4 (225.5 to 260.3)	486.3 (450.6 to 524.0)
Vaccine efficacy, % (95% CI)	50.2 (44.7 to 55.0)	N/A
Severe covid-19 infection:		
Number of incident cases	144	221
Incidence density per 1000 person-years, (95% CI)	46.1 (38.8 to 54.2)	156.2 (136.3 to 178.2)
Vaccine efficacy, % (95% CI)	70.5 (63.7 to 76.1)	N/A
Critical covid-19 infection:		
Number of incident cases	7	19
Incidence density per 1000 person-years, (95% CI)	2.2 (0.9 to 4.6)	13.4 (8.1 to 21.0)
Vaccine efficacy, % (95% CI)	83.1 (61.2 to 93.5)	N/A
Death due to covid-19:		
Number of incident cases	0	2
Incidence density per 1000 person-years (95% CI)	0	1.4 (0.2 to 5.1)
Vaccine efficacy, % (95% CI)	N/A	N/A

CI=confidence interval; N/A=not applicable.

between subgroups was not performed due to limited statistical power.

Safety was analysed among the safety population, defined as participants who received at least one dose of vaccine or placebo throughout the study. The exploratory humoral immunogenicity assessment was conducted for a subgroup of participants who had randomly received the vaccine or placebo with blood collection before and after each injection. We used frequency (percentage), mean, and standard deviation. The groups were compared with a two-sample t-test at a two-sided 5% significance level. The statistical analyses were carried out using R statistical packages version 3.4.3 (http://www.r-project.org, RRID: SCR_001905). Data visualisations were performed using Tableau Desktop, version 2020.1, an interactive data visualisation software.

Patient and public involvement

The data and places where the research took place were restricted and we lacked the permissions to engage patient and public involvement. Moreover, the study was initiated before patient and public involvement was common. Thus, the public was not involved in setting the research question, the outcome measures, the design, or implementation of the study.

Table 4 | Symptomatic covid-19 cases among study subgroups in the intervention and the placebo groups

Subgroups	Intervention group, n (%)	Placebo group, n (%)
Sex:		
Female	253 (5.7)	216 (9.7)
Male	505 (6.0)	253 (6.0)
Age groups:		
18-50 years	653 (6.1)	572 (10.6)
51-75 years	105 (4.7)	116 (10.9)
Location:		
Tehran	498 (8.9)	415 (15.8)
Mashhad	55 (3.0)	51 (5.5)
Isfahan	28 (1.6)	76 (8.8)
Shiraz	41 (2.7)	48 (6.3)
Karaj	97 (7.6)	74 (11.6)
Bushehr	39 (4.2)	24 (5.1)
Serology status:		
Seronegative	632 (6.7)	520 (10.8)
Seropositive	126 (3.6)	168 (10.3)
Comorbidity:		
Yes	53 (5.9)	52 (10.9)
No	705 (5.9)	636 (10.6)

Results

Characteristics of participants

Overall 64 049 volunteers in all study sites were screened for eligibility, and 20 000 were randomly assigned: 13 335 (66.7%) to the intervention group and 6665 (33.3%) to the placebo group (fig 2). All included participants received the first dose, among whom 19 506 (97.5%) received the second dose (13 011/13 335 (97.6%) in the intervention group and 6495/6665 (97.4%) in the placebo group). Of all participants, 6458/ 20 000 (32.3%) were seropositive for baseline IgG or IgM tests; of which 4305/13 335 (32.3%) were in the intervention and 2153/ 6665 (32.3%) were in the placebo group, which was excluded in the subclass analysis of vaccine efficacy. From participants who received both doses of vaccine/placebo, 105/19 506 (0.5%) were excluded due to deviation from the study protocol and data for 19 401/19 506 (99.5%) people (12 945 in the intervention group and 6456 in the placebo group) were analysed for vaccine efficacy (fig 2). All 20 000 participants who received at least one dose of vaccine or placebo were included in the safety population.

Participants' mean age was 38.3 years (standard deviation 11.2), and 6913 (34.6%) were female (table 2). Of the 20 000 recruited participants, 1428 (7.1%) had at least one coexisting underlying condition, with 932 (7.0%) of 13 335 in the intervention group and 496 (7.4%) of 6665 in the placebo group. Nearly 17% of participants in both intervention and placebo groups were older than 50 years. A total of 8716 (43.6%) participants included in the study were from Tehran, 2867 (14.3%) were from Mashhad, 2671 (13.4%) were from Isfahan, 2328 (11.6%) were from Shiraz, 1985 (9.9%) were from Karaj, and 1433 (7.2%) were from Bushehr.

Table 5 | Adverse reactions after administration of BIV1-CovIran or placebo in the safety population

	Intervention (n=13 335)		Placebo (n=6665)		Total (n=20 000)	
Adverse events	Events	Participants, n (%)	Events	Participants, n (%)	Events	Participants, n (%)
Adverse reactions						
Total	19 363	7960 (59.7)	9419	3816 (57.3)	28 782	11 776 (58.9)
Solicited	11 850	6129 (46.0)	5777	2932 (44.0)	17 626	9061 (45.3)
Unsolicited	7517	4277 (32.1)	3639	2099 (31.5)	11 156	6376 (31.9)
Systemic	12 866	5272 (39.5)	6402	2512 (37.7)	19 268	7784 (38.9)
Local	6497	5189 (38.9)	3017	2428 (36.4)	9514	7617 (38.1)
Grading of adverse reactions						
Grade 1	18 131	7820 (58.6)	8850	3773 (56.6)	26 981	11 593 (58.0)
Grade 2	1126	743 (5.6)	528	330 (5.0)	1654	1073 (5.4)
Grade 3	104	75 (0.6)	43	32 (0.5)	147	107 (0.5)
Grade 4	0 (0)	0 (0)	0	0 (0)	0	0 (0)
Serious adverse events*						
Total	85	83 (0.6)	79	74 (1.1)	164	157 (0.8)
Admission to hospital due to covid-19	47	47 (0.4)	53	51 (0.8)	100	98 (0.5)
Admission to hospital due to other reasons (PCR+)	5	4 (0.02)	8	7 (0.1)	13	11 (0.05)
Admission to hospital due to other reasons (PCR–)	23	22 (0.2)	12	10 (0.2)	35	32 (0.2)
Anaphylactic shock	1	1 (0.007)	0	0 (0)	1	1 (0.005)
Medically important event	9	9 (0.06)	6	6 (0.09)	15	15 (0.08)

PCR+=positive real-time reverse transcription polymerase chain reaction for SARS-Cov-2 infection; PCR–=negative real-time reverse transcription polymerase chain reaction for SARS-Cov-2 infection.
*Supplementary table S3 presents the complete list of serious adverse events during the study.

Vaccine efficacy

Primary efficacy endpoint analysis

Of 19 401 participants in the efficacy population, 1446 (7.5%) had symptoms of covid-19 confirmed during the 90 day follow-up after 14 days from administration of the second dose (median follow-up duration of 83 days), with 758/12 945 (5.9%) in the intervention group and 688/6456 (10.7%) of 1446 in the placebo group. The incidence rate of covid-19 was 242.4 (95% confidence interval 225.5 to 260.3) per 1000 person-years in the intervention group and 486.3 (450.6 to 524.0) per 1000 person-years in the placebo group. This case split corresponds to 50.2% (44.7% to 55.0%) vaccine efficacy against symptomatic covid-19 infection. Of 19 401 participants, 365 (1.9%) participants met the criteria of severe covid-19, with 144/12 945 (1.1%) in the intervention group. This case split corresponds to 70.5% (63.7% to 76.1%) vaccine efficacy. Among participants, seven cases of critical covid-19 with onset 90 day follow-up after 14 days from the administration of the second dose were observed among vaccine recipients and 19 were observed among placebo recipients. This case split corresponds to 83.1% (61.2% to 93.5%) vaccine efficacy. No deaths were due to covid-19 with onset 90 day follow-up among vaccine recipients, whereas two people died due to covid-19 among the placebo recipients. Considering the small number of incident death cases, these results must be interpreted with caution (table 3).

Post hoc analysis

A similar number of covid-19 symptomatic cases were observed for men and women (table 4). Of all critical cases, five were female, one in the intervention group and four in the placebo group. Among men with critical covid-19, six were in the intervention group and 15 were in the placebo group. Considering the limited statistical power, the interpretation of these findings was not possible.

Among participants aged 51-75 years, 221 people had positive covid-19 RT-PCR test consisting of 105 among vaccinated participants. Only two participants aged 51-75 years were included in the critical covid-19 cases.

Among participants aged 65-75 years, 46 (16.7%) symptomatic covid-19 cases were recorded, with only eight (17.4%) in the intervention group. The vaccine efficacy among participants aged 65-75 years for symptomatic covid-19 was 90.7% (95% confidence interval 81.0% to 96.0%). Among participants aged 65-75 years, 18 cases of covid-19 were severe and one case was critical. Interpretation of these subgroup findings is limited in the absence of tests for interaction due to limited statistical power.

The number of symptomatic covid-19 events for each location is presented in table 4. No deaths due to covid-19 occurred among vaccinated participants in either group of sex, age, and location; thus, efficacy was not calculated. Given the serology status of phase 3 participants, the vaccine efficacy among seronegative participants was 42.9% (95% confidence interval 35.8% to 49.1%) against symptomatic covid-19 infection, 63.7% (54.0% to 71.4%) against severe infection, and 82.9% (54.7% to 94.6%) against critical infection (supplementary appendix 2: table S1).

Vaccine safety

Local and systemic adverse events in the intervention and placebo groups are presented in table 5. During follow-up, 41 922 adverse events were reported, of which 28 782 (68.7%) were adverse reactions; and of these, 19 363 (67.3%) were in the intervention group. As many as 17 626 (61.2%) adverse reactions were

Table 6 | Exploratory immunogenicity assessment two weeks after the second dose among 400 participants of phase 3

	Geometric mean titre (µg/ml) (95% CI)			Seroconversion rate,* % (95% CI)	
Antibody	5 µg	Placebo	Geometric mean ratio, 5 µg (95% CI)	5 µg	Placebo
Neutralising antibody					
Day 0	1.4 (1.3 to 1.6)	1.4 (1.1 to 1.6)	1.1 (0.9 to 1.3)	–	–
Day 42	6.0 (5.0 to 7.1)	0.9 (0.7 to 1.1)	6.6 (5.0 to 8.8)	64.4 (58.3 to 70.2)	8.1 (4.1 to 14.0)
Difference†	4.18 (3.39 to 5.16)	0.66 (0.52 to 0.84)	N/A	N/A	N/A
Anti-receptor binding domain IgG					
Day 0	0.5 (0.4 to 0.6)	0.6 (0.3 to 0.5)	1.3 (0.9 to 1.8)	–	–
Day 42	8.3 (7.5 to 9.2)	0.6 (0.4 to 0.8)	15.0 (11.6 to 19.6)	66.3 (60.2 to 72.0)	14.7 (9.2 to 21.8)
Difference	17.64 (14.01 to 22.42)	1.48 (1.02 to 2.12)	N/A	N/A	N/A
Anti-spike glycoprotein IgG					
Day 0	1.2 (0.9 to 1.6)	1.4 (0.9 to 2.2)	0.9 (0.5 to 1.5)	–	–
Day 42	49.4 (43.7 to 55.9)	1.3 (0.8 to 2.0)	38.4 (26.8 to 54.9)	71.2 (65.3 to 76.6)	14.0 (8.6 to 21.0)
Difference	41.68 (29.67 to 58.56)	0.92 (0.55 to 1.55)	N/A	N/A	N/A

Results were reported at baseline (day 0) and two weeks after the second vaccination (day 42) for 5 µg and placebo groups. N/A=not applicable.
*Defined as a post-vaccination IgG titre that was at least fourfold higher than the baseline titre. Geometric mean titres for neutralising antibodies are reported in µg/mL anti-receptor binding domain IgG in RU/mL and anti-spike glycoprotein IgG RU/mL.
†Paired t-test with log-transformed values, difference, and 95% confidence interval back-transformed.

solicited consisting of 11 850 (61.2%) of 19 363 in the intervention group and 5777 (61.3%) of 9419 in the placebo group.

Of all 20 000 participants, adverse reactions occurred among 11 776 (58.9%) participants, with 7960 (59.7%) of 13 335 in the intervention group and 3816 (57.3%) of 6665 in the placebo group. The most common local adverse reaction among phase 3 participants was pain in the injection site, which accounted for 38.0% of all total adverse reactions in the intervention group and 35.5% in the placebo group. Headache with 12.3% of total adverse reactions in the intervention group and 12.4% in the placebo group, was considered the most common systemic adverse reaction among phase 3 participants. Most adverse reactions were mild or moderate in severity (grade 1 or 2) and were transient and self-limiting, without the need for special consideration (table 5 and supplementary table S2). The mean number of days to resolve the adverse reactions was 2.7 (standard deviation 4.9).

A total of 164 serious adverse events (all causes) occurred during follow-up, with 85 (51.8%) occurrences in the intervention group (supplementary table S3). No serious adverse events were considered to be related to the injections. Throughout the three month follow-up of phase 3 participants, five deaths due to covid-19 infection were reported, of which two were in the efficacy population (supplementary table S4).

Exploratory immunogenicity analysis

Among 400 vaccinated participants who were selected for exploratory immunogenicity analysis, the geometric mean titres of the neutralising, anti-receptor binding domain and anti-S glycoprotein antibodies at baseline in the intervention group were 1.4 (95% confidence interval 1.3 to 1.6), 0.5 (0.4 to 0.6), and 1.2 (0.9 to 1.6), respectively; while the corresponding rates were 6.0 (5.0 to 7.1), 8.3 (7.5 to 9.2) and 49.4 (43.7 to 55.9) on day 42. In the placebo group, the geometric mean titres for neutralising, anti-receptor binding domain, and anti-S glycoprotein antibodies at the baseline were 1.4 (1.1 to 1.6), 0.6 (0.3 to 0.5), and 1.4 (0.9 to 2.2), respectively. On day 42, the corresponding geometric mean titres were 0.9 (0.7 to 1.1), 0.6 (0.4 to 0.8), and 1.3 (0.8 to 2.0), respectively. The seroconversion rate for neutralising antibodies was 64.4% (58.3% to 70.2%) in the intervention group versus 8.1% (4.1% to 14.0%) in the placebo group (table 6, fig 3). The exploratory immunogenicity

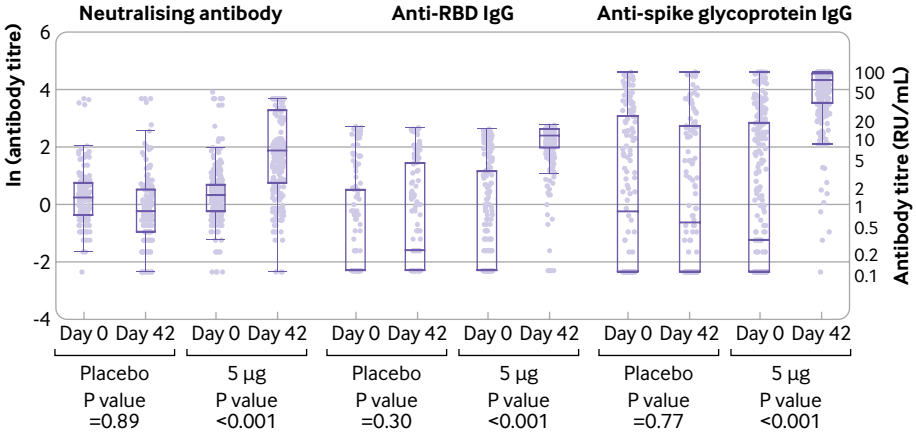


Fig 3 | Anti-SARS-CoV-2 antibody titres for neutralising, anti-receptor binding domain, and anti-spike antibodies in phase 3. Data points and quartiles are presented in box plots. ln=natural logarithm; RBD=receptor binding domain

analysis results among seronegative participants are presented in supplementary table S5.

Dominant variant

Among 151 samples, 119 (78.8%) samples were positive for SARS-CoV-2, and 32 (21.2%) were negative. When checked for the SARS-CoV-2 variant, 106 samples (89.1%) were positive for the delta variant; six (5.0%) for the Wuhan variant; six (5.0%) for the alpha variant, and one (0.8%) for gamma, lambda, or beta variant.

Discussion

Main findings

This study presents the findings from the phase 3 clinical trial of BIV1-CovIran, an inactivated whole virus particle vaccine for SARS-CoV-2, adjuvanted with aluminium hydroxide. Vaccine efficacy was assessed during a 90 day follow-up following 14 days after the second dose. Based on the final per-protocol analysis, a two-dose regimen of the vaccine (5 µg per dose, given 28 days apart) was well tolerated, induced significant seroconversion, was 50% effective against symptomatic covid-19, and was 83% effective against critical covid-19. Moreover, no deaths were recorded in the vaccine group during the follow-up period. Our preliminary vaccine efficacy against symptomatic covid-19 infection was 50%, with a vaccine efficacy of 91% among participants aged 65-75 years. Thus, the vaccine efficacy greatly exceeded the primary efficacy endpoints as set by WHO.[16]

Comparison with other studies

The favourable safety profile of BIV1-CovIran observed in the phase 1 and phase 2 clinical trials[8] was confirmed in phase 3. In this study, no safety concerns were raised, no anaphylactic events after BIV1-CovIran administration were reported, and all adverse events (solicited, unsolicited, and serious adverse events) were well balanced between the intervention and placebo groups. The most common adverse event was injection site pain, followed by headache. Overall, 164 serious adverse events were reported during the trial, of which 85 were in the intervention group, and all were not related to the vaccine. Serious adverse events in this study were defined as death, life-threatening events, admission to hospital due to any cause, prolonged stay in hospital period, and any other conditions deemed serious by the principal investigator. As presented in supplementary table S3, 100 of 164 serious adverse events were admitted to hospital due to covid-19: 53 in the placebo group and 47 in the intervention group. A potential explanation for the higher rates of serious adverse events in the placebo group could be the partial protection against being admitted to hospital among participants who received the vaccine. The combined incidence of local and systemic adverse events after both vaccine doses in this study was similar to that of other inactivated SARS-CoV-2 vaccines,[17-21] and lower than that of other SARS-CoV-2 vaccine platforms.[22-27] Nevertheless, such a comparison of adverse events among vaccines of different platforms needs to be interpreted with caution, and further studies are required for a head-to-head comparison of the short term and long term safety across all SARS-CoV-2 vaccine platforms.

This phase 3 study was done during a period that included the fifth wave of covid-19 infections in Iran, mainly consisting of the delta variant of SARS-CoV-2, with a peak of more than 50 000 new cases per day.[10 28] The emergence of the delta variant rapidly resulted in a large increase in covid-19 cases worldwide[28] as well as in hospital admissions, far beyond what had already been reported with the alpha variant. Evidence suggests that the substantial mutations[29] have resulted in increased transmission[30] of the delta variant. Moreover, some mutations could inversely affect the host's immune responses.[31] While the unvaccinated populations were the most at risk of infection from the delta variant,[6] the effectiveness of covid-19 vaccines was also challenged, especially after receiving a single dose.[32] When a subsample of participants with symptomatic covid-19 were assessed for the delta variant, 89.1% were positive for the delta variant, suggesting that the dominant variant was the delta variant during the study. In our preliminary analysis, we recorded a vaccine efficacy of 50% against symptomatic covid-19, and 83% against critical covid-19 at the time of study. Assuming that the dominant variant was delta during the study, BIV1-CovIran could have had an acceptable efficacy against this variant. Nevertheless, further investigations are necessary to confirm clinical efficacy against this and other potential SARS-CoV-2 variants in the future.

Initially reported in late 2021, the highly contagious B.1.1.529 (omicron) variant of concern has globally outcompeted the earlier variants with its higher rates of spike protein mutation, resulting in higher immune evasion capacity.[33 34] The omicron variant has reportedly challenged the effectiveness and neutralisation capacity of SARS-CoV-2 vaccines, developed initially against the Wuhan variant.[33 35-38] Among the potential mitigating strategies for omicron or future variants of concern, choosing between delivering booster doses of conventional covid-19 vaccines, homologous or heterologous doses,[39] and developing vaccine boosters on omicron[40-42] is an ongoing debate that needs extensive investigation in the future studies.

Our efficacy and safety findings were similar to previous results of two other alum-adjuvanted inactivated SARS-CoV-2 vaccines, which both showed vaccine efficacy against critical cases at 78%.[21 43] Thus, full vaccination with BIV1-CovIran could potentially result in a marked reduction of cases with critical covid-19 and death due to covid-19, which put a tremendous burden on healthcare systems and take a heavy toll on populations.

Strengths and limitations

Based on the follow-up data, BIV1-CovIran was safe and effective against SARS-CoV-2 infection, preventing

severe and critical cases. Considering the great toll of covid-19 in Iran and the emerging evidence of the need for booster doses,[44] the public rollout of a safe domestic covid-19 vaccine could be a valuable solution. We also acknowledge the limitations of the study. Mass and social media platforms were used to attract the participation of eligible individuals in the study. As such, at the recruiting phase of this trial, less than 3% of the Iranian population had been fully vaccinated for covid-19. Thus, people would have been hypervigilant regarding covid-19 vaccination. Some people would have been eager to participate in a domestic covid-19 vaccine trial and would have followed the news on mass and social media. Participation in the study was also widely discussed on television and radio. Additionally, we acknowledge that this study could be subject to selection bias, although the internet penetration rate exceeds 84% in Iran.[45] This study presents the results of a three-month follow-up after the second dose of BIV1-CovIran. Thus, the occurrence of adverse events beyond the study period and evidence on efficacy and the duration of protection remain to be determined in future studies. Since vaccine efficacy tends to wane over time,[46] the efficacy estimates would likely drop if the trial had a longer follow-up time. Nevertheless, this needs further investigation in future studies. The phase 3 trial was designed to follow participants for safety and efficacy for 365 days after the second dose (supplementary appendix 1). However, ethical considerations prevented following up recipients of the placebo for 365 days without active immunisation. Once approved vaccines for covid-19 were publicly available, the national ethical committee required all clinical trials for covid-19 vaccines to decode their data and notify participants in the placebo group to get vaccinated for covid-19, after three months of the second placebo administration. Subsequently, participants in the placebo group were administered the currently available covid-19 vaccines, including BIV1-CovIran, BBIBP-CorV, ChAdOx1 nCoV-19, PastoCoAd, and SpikoGen. We initially aimed to present the interim analysis based on the 180 day follow-up, as stated in the study protocol. After the request of the ethical committee, we provided the interim report for the Iranian Food and Drug Administration based on a shorter follow-up period (median 83 days) after the second dose, the results of which are presented in this study. The median follow-up duration of other covid-19 vaccine phase 3 trials after the second dose was 99 days for BBV152,[21] 112 days for BBIBP-CorV,[47] 61 days for ChAdOx1 nCoV-19,[48] two months for ChAdOx1 nCoV-19,[26] and six months for BNT162b2.[49] Moreover, this follow-up was 90 days after the first dose for CoronaVac.[50] The study did not have enough power to assess efficacy by subgroup definitively. Despite being a multicentre trial, all the clinical trial phases of BIV1-CovIran have been conducted in Iran. We reported the immunogenicity of the vaccine candidate in phase 1/2 studies.[8] In this phase 3 trial, we assessed the exploratory immunogenicity response of 400 participants using the convenience sampling method. Therefore, the results might not be representative of the general population, which needs to be assessed in future studies. The vaccine has not been studied on ethnic groups beyond the Iranian population, which needs to be addressed in future studies. The study population also lacked ethnic and racial diversity, highlighting the importance of evaluating the efficacy of BIV1-CovIran in other populations. This report does not address the prevention of covid-19 in different populations, such as younger adolescents, children, and pregnant women. Given the occurrence of the SARS-CoV-2 delta variant amid this phase 3 trial,[10] variant detection was conducted in the study. Due to resource constraints in other trial sites, this procedure was only available in Tehran, the main trial site with 43.6% of participants. Using the convenience sampling method, 151 samples were obtained from 913 participants at the Tehran trial site who became symptomatic of covid-19 and underwent variant detection.

Conclusions

BIV1-CovIran had high efficacy against severe and critical covid-19. Vaccination was well tolerated, with no safety concerns raised.

AUTHOR AFFILIATIONS

[1]Iranian Research Center for HIV/AIDS, Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran

[2]The Persian Gulf Tropical Medicine Research Center, The Persian Gulf Biomedical Sciences Research Institute, Bushehr University of Medical Sciences, Bushehr, Iran

[3]Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

[4]Department of Pharmaceutics, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

[5]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

[6]Department of Pharmaceutics, Faculty of pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran

[7]Department of Hepatitis and AIDS, Pasteur Institute of Iran, Tehran, Iran

[8]Amirabad Virology Laboratory, Vaccine Unit, Tehran, Iran

[9]School of Medicine, Shahroud University of Medical Sciences, Semnan, Iran

[10]Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Disease, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[11]Non-Communicable Diseases Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[12]Acquired Immunodeficiency Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

[13]Department of Infectious Diseases and Tropical Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[14]Department of Infectious Diseases and Tropical Medicine, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

[15]Center for Research and Training in Skin Diseases and Leprosy, Tehran University of Medical Sciences, Tehran, Iran.

[16]Clinical Trial Center, Tehran University of Medical Sciences, Tehran, Iran

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: As the principal investigator, Minoo Mohraz declares that a research contract between Shifa-Pharmed (sponsor) and Iranian Research Centre for HIV/AIDS (IRCHA) for supervising all clinical trial activities was signed, and the contract sum was deposited into the account number of this centre at Tehran University of Medical Sciences. Minoo Mohraz's position at the time was director of this centre; as such, the payment appears to be transferred to her name in Shifa-Pharmed's financial statements. Asghar Abdoli is the founder and the scientific director of Amirabad Virology Laboratory and the only shareholder of this laboratory. He is a faculty member of the Pasteur Institute of Iran and was also a project consultant for the PastoCoAd vaccine project, which was initiated after the BIV1-CovIran vaccine project. Payam Tabarsi was the principal investigator of another SARS-CoV-2 vaccine trial, SpikoGen. Hamed Hosseini was the manager of the Clinical Trial Center, an academic contract research organization affiliated to 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 the data safety and monitoring board, which was mandated by national regulatory. 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.

Ethical approval: The study protocol was approved by the National Research Ethics Committee under the reference code of IR.NREC.1399.008, and was registered at the Iranian Registry of Clinical Trials (IRCT20201202049567N3).

Data sharing: 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.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Web appendix: Study protocol
Web appendix: Extra material on adverse events and exploratory analysis