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Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey



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Summary

Background CoronaVac, an inactivated whole-virion SARS-CoV-2 vaccine, has been shown to be well tolerated with a good safety profile in individuals aged 18 years and older in phase 1/2 trials, and provided a good humoral response against SARS-CoV-2. We present the interim efficacy and safety results of a phase 3 clinical trial of CoronaVac in Turkey.

Methods This was a double-blind, randomised, placebo-controlled phase 3 trial. Volunteers aged 18–59 years with no history of COVID-19 and with negative PCR and antibody test results for SARS-CoV-2 were enrolled at 24 centres in Turkey. Exclusion criteria included (but were not limited to) immunosuppressive therapy (including steroids) within the past 6 months, bleeding disorders, asplenia, and receipt of any blood products or immunoglobulins within the past 3 months. The K1 cohort consisted of health-care workers (randomised in a 1:1 ratio), and individuals other than health-care workers were also recruited into the K2 cohort (randomised in a 2:1 ratio) using an interactive web response system. The study vaccine was 3 µg inactivated SARS-CoV-2 virion adsorbed to aluminium hydroxide in a 0.5 mL aqueous suspension. Participants received either vaccine or placebo (consisting of all vaccine components except inactivated virus) intramuscularly on days 0 and 14. The primary efficacy outcome was the prevention of PCR-confirmed symptomatic COVID-19 at least 14 days after the second dose in the per protocol population. Safety analyses were done in the intention-to-treat population. This study is registered with ClinicalTrials.gov (NCT04582344) and is active but no longer recruiting.

Findings Among 11 303 volunteers screened between Sept 14, 2020, and Jan 5, 2021, 10 218 were randomly allocated. After exclusion of four participants from the vaccine group because of protocol deviations, the intention-to-treat group consisted of 10 214 participants (6646 [65.1%] in the vaccine group and 3568 [34.9%] in the placebo group) and the per protocol group consisted of 10 029 participants (6559 [65.4%] and 3470 [34.6%]) who received two doses of vaccine or placebo. During a median follow-up period of 43 days (IQR 36–48), nine cases of PCR-confirmed symptomatic COVID-19 were reported in the vaccine group (31.7 cases [14.6–59.3] per 1000 person-years) and 32 cases were reported in the placebo group (192.3 cases [135.7–261.1] per 1000 person-years) 14 days or more after the second dose, yielding a vaccine efficacy of 83.5% (95% CI 65.4–92.1; $p < 0.0001$). The frequencies of any adverse events were 1259 (18.9%) in the vaccine group and 603 (16.9%) in the placebo group ($p = 0.0108$) with no fatalities or grade 4 adverse events. The most common systemic adverse event was fatigue (546 [8.2%] participants in the vaccine group and 248 [7.0%] the placebo group, $p = 0.0228$). Injection-site pain was the most frequent local adverse event (157 [2.4%] in the vaccine group and 40 [1.1%] in the placebo group, $p < 0.0001$).

Interpretation CoronaVac has high efficacy against PCR-confirmed symptomatic COVID-19 with a good safety and tolerability profile.

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Introduction

The COVID-19 pandemic continues to affect individuals and populations, magnifying socioeconomic and health inequalities globally.^{1–4} Vaccination is a crucial measure in breaking the transmission chain of SARS-CoV-2 infections. Among several vaccines against SARS-CoV-2, 13 in clinical development are inactivated vaccines, two of

which are already in phase 4 trials. Although the basic cultivation techniques using Vero cells and inactivation strategies are similar, inactivated vaccines differ in the isolated virion strains and the adjuvants used.^{5,6} The potential advantages of inactivated vaccines are non-replicability in the host, non-transmissibility, and the induction of a broad range of humoral and cellular

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Research in context

Evidence before this study

We searched PubMed for research articles published up to April 28, 2021, with no language restrictions, using the terms “SARS-CoV-2” OR “COVID-19” AND “vaccine” AND “clinical trial” AND “efficacy”. We found four articles reporting the interim efficacy and safety results of phase 3 trials: ChAdOx1 nCoV-19 vaccine (University of Oxford–AstraZeneca) showing an efficacy against symptomatic COVID-19 of 62.1% (95% CI 41.0–75.7) with two standard doses and 90.0% (67.4–97.0) with a low dose followed by a standard dose; Gam-COVID-Vac (Gamaleya National Research Centre for Epidemiology and Microbiology) showing an efficacy of 91.6% (85.6–95.2); mRNA-1273 SARS-CoV-2 vaccine (Moderna) showing an efficacy of 94.1% (89.3–96.8), and BNT162b2 mRNA COVID-19 vaccine (Pfizer–BioNTech) showing an efficacy of 95% (90.3–97.6). The results of the ENSEMBLE trial showed that the efficacy of a single dose of the Ad26.COV2.S vaccine (Janssen Research and Development) against moderate to severe or critical COVID-19 with onset at least 14 days after administration was 66.9% (adjusted 95% CI 59.0–73.4) and at least 28 days after administration was 66.1% (55.0–74.8), and higher efficacies were obtained for severe or critical COVID-19. In the world’s first publicly reported animal trial of a SARS-CoV-2 candidate vaccine PiCoVacc, thereafter named CoronaVac in clinical trials, Gao and colleagues showed that the vaccine induced the production of SARS-CoV-2-specific neutralising antibodies in animals and provided complete protection against SARS-CoV-2 challenge in non-human primates. Phase 1/2 studies of CoronaVac showed a good safety and tolerability profile, and a dosage of 3 µg produced seroconversion rates of 92.0% with a 14-day immunisation schedule and 97.0% with a 28-day schedule in participants aged 18–59 years, and 98.0% with a 28-day schedule in participants aged 60 years and older in phase 2 trials.

Added value of this study

This study reports the interim analysis of a double-blind, randomised, placebo-controlled phase 3 clinical trial to assess the efficacy and safety of the inactivated and aluminium hydroxide-adsorbed SARS-CoV-2 vaccine in Turkey, in which both high-risk health-care workers and volunteers with an average COVID-19 exposure risk in the community were recruited. CoronaVac showed an efficacy of 83.5% for preventing PCR-confirmed symptomatic COVID-19, with no cases of COVID-19 requiring hospitalisation. The incidence of adverse events was low (18.9%). Preliminary immunogenicity results revealed that CoronaVac induced anti-receptor-binding domain antibodies in 89.7% of participants. The vaccine is stored and transported at 2–8°C and was granted emergency use authorisation for mass vaccination in Turkey on Jan 13, 2021.

Implications of all the available evidence

The world needs every possible dose of any safe and effective vaccine against SARS-CoV-2. Although novel genetic vaccine production platforms hold great potential for the rapid and adaptable mass production of vaccines, traditional platforms have a long experience of producing safe and tolerable vaccines with good immunogenicity. The results of this interim analysis have shown that CoronaVac fulfils the critical or minimal requirement of vaccines for the indication of pandemic use, hitting above the minimum efficacy of 50% as specified by the WHO target product profile as an option for mass vaccination. WHO has given emergency use approval to another inactivated vaccine from a different Chinese producer (Sinopharm-Beijing) and our results add to the existing evidence on safety and efficacy of inactivated vaccines for prevention of COVID-19.

responses against different epitopes. Their production and scale-up are relatively easy in the context of good yield production systems and the availability of biosafety level 3 facilities.⁷ Disadvantages include limited immunogenicity requiring adjuvants to enhance the immune response, large quantities of live virus to be handled, and the integrity of antigens or epitopes that should be verified.⁸

CoronaVac, an inactivated whole-virion SARS-CoV-2 vaccine candidate developed by Sinovac Life Sciences (Beijing, China), has been in phase 3 trials since mid-2020 in Brazil, Indonesia, Chile, and Turkey. As of April 28, 2021, it has been approved in 22 countries for emergency use.⁹ In this Article, we present the interim safety and efficacy results of a phase 3 trial in Turkey investigating the use of CoronaVac in adults.

Methods

Study design and participants

We did a double-blind, randomised, placebo-controlled, case-driven phase 3 clinical trial to assess the safety and

efficacy of the inactivated SARS-CoV-2 vaccine CoronaVac among volunteers in Turkey.

Volunteers aged 18–59 years with no history of COVID-19 were screened for eligibility. Exclusion criteria included (but were not limited to) positive PCR and total antibody tests for SARS-CoV-2; pregnancy, breastfeeding; known allergy to components of the study vaccine or placebo; recent (within the past 6 months) or planned use of immunosuppressive therapy, or use of immunoglobulins or any blood products within the past 3 months; asplenia; history of bleeding disorder; alcohol or drug abuse; and any confirmed or suspected autoimmune or immunodeficiency disease. The study protocol containing the full list of eligibility criteria is available online.¹⁰

Participants were recruited in two consecutive cohorts (K1 and K2) at 24 centres (appendix p 8) in Turkey between Sept 15, 2020, and Jan 6, 2021. K1 included actively working health-care workers such as doctors, nurses, and technicians working in health-care facilities,

including but not confined to COVID-19 areas, and was launched to closely observe the safety of the vaccine before proceeding with the community. K2 included subjects representing the community in addition to health-care workers included in K1.

During the study, the Ministry of Health gave an emergency use authorisation for CoronaVac on Jan 13, 2021, and started an immediate vaccination programme initially for health-care workers and later for the public, prioritising older adults (aged ≥ 65 years). Although recruitment of volunteers was ongoing at this time, to comply with the principles of the Declaration of Helsinki regarding using a placebo for human subjects in medical research, the ethics committee suggested discontinuing the masking and injection of participants in the placebo group. Consequently, the placebo recipients were offered vaccines, first in K1 and later in K2.

The study protocol was approved by the clinical research ethics board of Hacettepe University (approval number 2020/10-26, July 16, 2020). The entire study protocol was published previously and is available on the Hacettepe University Vaccine Institute website.¹⁰ Signed informed consent was obtained from participants before screening.

Randomisation and masking

Randomisation into vaccine and placebo groups was done on day 0, at a 1:1 ratio in K1 and a 2:1 ratio in K2, using an interactive web response system (Omega-CRO, Ankara, Turkey). Participants and practitioners were masked to the group allocation. The masking was removed in the event of a medical emergency requiring acute intervention, upon the responsible investigator's approval and the data and safety monitoring board's knowledge.

Procedures

Oropharyngeal and nasopharyngeal swabs were obtained from all participants for baseline PCR testing with a Bio-Speedy Direct RT-qPCR SARS-CoV-2 detection kit (Bioeksan, Istanbul, Turkey) on a Bio-Rad CFX96 Touch platform (Hercules, CA, USA), and serum total SARS-CoV-2 antibody testing was done. The ADVIA Centaur COV2T assay (Siemens Healthcare Diagnostics, Erlangen, Germany), a fully automated one-step antigen sandwich immunoassay using acridinium ester chemiluminescence technology, was used to detect total antibodies (IgG and IgM) against the SARS-CoV-2 spike protein receptor-binding domain (RBD) in serum samples. This assay is semiquantitative and has a lower detection threshold value (1 sample-to-cutoff ratio). All PCR and serum antibody tests were done at two central laboratories.

The study vaccine is an inactivated whole-virion vaccine with aluminium hydroxide as the adjuvant, prepared with a novel coronavirus (CZ02 strain) inoculated in African green monkey kidney cells

(Vero cells). The inactivation process is done by adding β -propiolactone in the virus harvest fluid at a ratio of 1:4000 and inactivating at 2–8°C for 12–24 h. One dose of COVID-19 vaccine contains 3 μ g of SARS-CoV-2 virion in a 0.5 mL aqueous suspension for injection with 0.45 mg/mL of aluminium. The placebo contained all ingredients except the inactivated virus, in prefilled syringes. The injections were given in two doses, 14 days apart, intramuscularly in the deltoid muscle. As the placebo and study vaccine looked exactly the same, they were administered by staff masked to group allocation. Details of the procedures on visit dates and the pharmacological properties of the investigational product are provided in the appendix (pp 1–2).

Symptom-based active surveillance was done to detect participants with symptoms suggestive of COVID-19 during follow-up (appendix pp 3–4). Anyone with at least one of the following symptoms for 2 days or more underwent PCR testing: fever or chills; cough; dyspnoea; fatigue; muscle or body pain; headache; new loss of sense of smell or change in taste; sore throat; nasal congestion or rhinorrhoea; nausea or vomiting; and diarrhoea. Cases of SARS-CoV-2 infection were classified according to the scale of clinical progression proposed by WHO.¹¹ Clinical outcomes were assessed in a blinded manner.

Sampling for immunogenicity analyses was planned in a subgroup of volunteers selected sequentially. As the immunogenicity and T-cell response analyses are ongoing, we only report the initial results of the anti-RBD antibody tests and neutralising antibody assays gathered at least 14 days after the second dose of vaccine or placebo. Virus neutralisation assays were done in an in-house microtitre plate, as described by Hanifehnezhad and colleagues.¹² Five-fold diluted serum samples, starting from 1:5, were mixed with an equal volume of 100 median tissue culture infectious dose of SARS-CoV-2 Ankl1 isolate (1:10 000) in quadruplicate and incubated for 1 h at 37°C for neutralisation. The serum–virus mixtures were subsequently inoculated onto 90% confluent Vero E6 cells grown in 96-well plates. The assay was evaluated via inverted microscope when a 100% cytopathic effect was observed in the virus control wells. Reciprocals of serum dilutions inhibiting at least 50% of virus infectivity were expressed as mean antibody titre (SN_{50}).

Outcomes

The primary outcome was the incidence of symptomatic COVID-19 cases confirmed by RT-PCR at least 14 days after the second dose of vaccination, assessed in the per protocol population. Secondary outcomes were the incidence of symptomatic COVID-19 cases confirmed by RT-PCR at least 14 days after the first dose (assessed in all participants who received at least one dose); incidence of hospitalisation or mortality at least 14 days after the second dose; the incidence of COVID-19 cases confirmed by RT-PCR at least 14 days after the second dose; the seroconversion rate, seropositivity rate, geometric mean

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See Online for appendix

titre or geometric mean increase in neutralising antibody and IgG 14 days and 28 days after each dose; the incidence of adverse reactions from the day of first vaccination to 28 days after the second dose; the incidence of adverse reactions and adverse events within 7 days after each dose; and the incidence of serious adverse events from the first vaccination to 1 year after the second dose (appendix pp 5–7).

For evaluating the efficacy of CoronaVac, COVID-19-free person-years were calculated for both study groups. Accordingly, the time from the anticipated date of prevention (14 days after the administration of the second

dose) to either the date of unmasking or date of an RT-PCR-confirmed diagnosis of COVID-19 was ascertained for each participant and summed to calculate the total person-years without the disease. Total person-years were divided by the number of participants diagnosed with COVID-19 to ascertain the vaccine efficacy in intervention and placebo groups.

Participants were questioned about all adverse events during all visits and through automated phone calls via an interactive voice response system (appendix pp 3–4). Predefined symptoms (solicited events) and other unspecified symptoms (unsolicited events) reported by the participants were recorded. All adverse events were assessed by study investigators for severity and causality. Any adverse event assessed by study investigators as possibly, probably, or definitely related to a study product was defined as an adverse reaction. All safety data, until the date of unmasking and data cutoff, were recorded and analysed in the current report. Further safety data are still being obtained in an open-label follow-up study.

Statistical analysis

For K1, the estimated sample size in both study groups was 588, based on assumptions that the risk of infection with SARS-CoV-2 would be 5% for the placebo group and 2% for the vaccine group. Considering a 10% dropout rate and 5% baseline seropositivity or RT-PCR positivity, it was calculated that 680 subjects would be screened in both groups of K1. Total sample sizes were calculated as 7545 for the vaccine group and 3773 for the placebo group in order to be able to detect a minimum clinically significant difference of 1% (with estimated incidence rates of 1% for the vaccine group and 2% for the placebo group) in a two-sided hypothesis testing design with 95% CIs. With the addition of a 10% dropout rate and 5% seropositivity or RT-PCR positivity at baseline, the total sample size was determined to be 13 000 participants, of whom 1360 would be in K1 and 11 640 in K2.

The initial study protocol indicated that if the efficacy of the vaccine could be demonstrated with an interim analysis done with 40 confirmed cases of COVID-19, masking would be removed and participants in the placebo group would be offered CoronaVac. Because the study was initiated with health-care workers at high risk, it was estimated that 5% of the placebo group (29 participants) and 2% of the vaccine group (11 participants) would have to be infected to demonstrate a clinical efficacy of 60%. If those rates could not be obtained in K1, enrolment would begin for K2. The enrolment rate remained very low for K1 and, after an interim safety analysis on Nov 18, 2020, the data and safety monitoring board decided to start enrolment into K2. Although the prespecified number of COVID-19 cases for the interim efficacy analysis was 40, as the incidence throughout Turkey increased rapidly, the Ministry of Health asked for a preliminary analysis to be able to grant an emergency use authorisation for

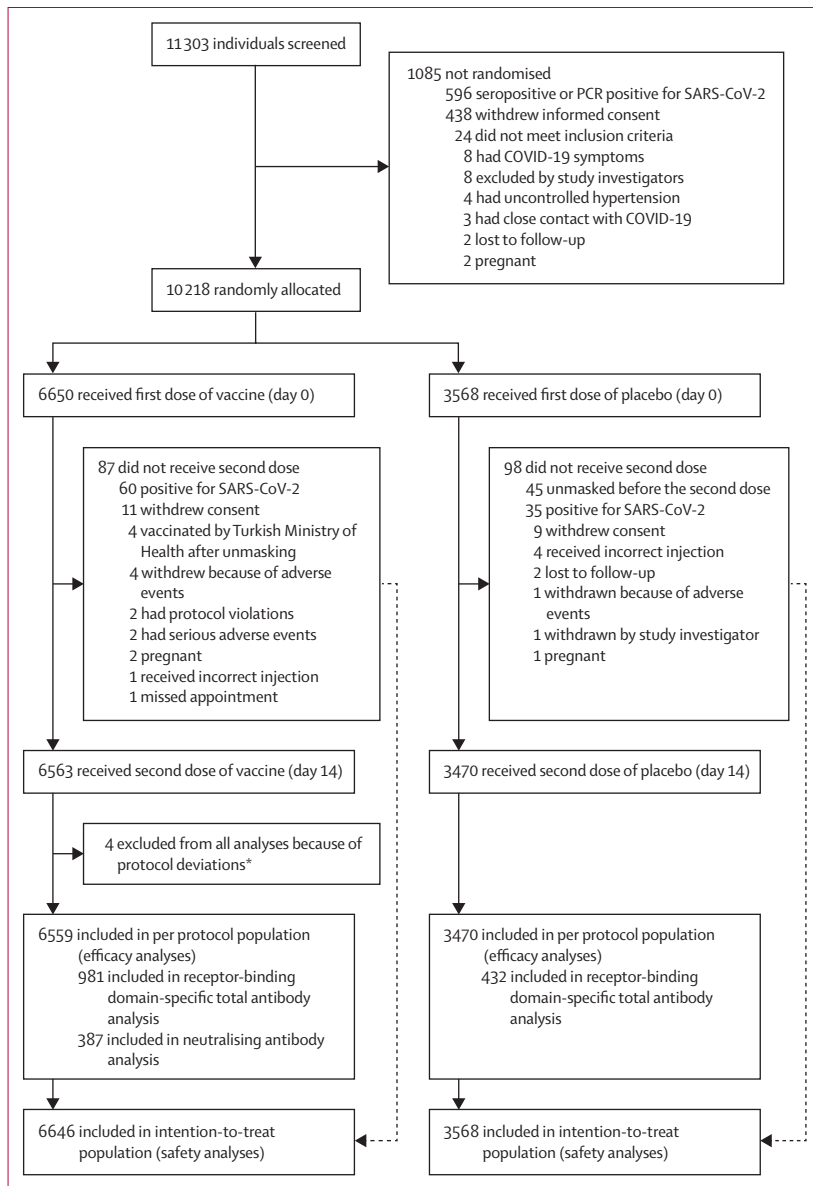


Figure 1: Trial profile

*Four participants in the vaccine group received two doses of the study product; however, because they were older than 59 years on the day of randomisation, they were excluded from all safety and efficacy analyses due to protocol violation.

CoronaVac. Therefore, a non-predefined interim analysis was done on Dec 24, 2020, with 29 cases, which showed an efficacy above 60%. Afterwards, as community vaccination commenced, study participants were unmasked starting with K1 in blocks. The masked follow-up of those participants continued until their code was unmasked, and 41 COVID-19 cases were attained by the time all of the codes were unmasked and the prespecified interim analyses for efficacy and safety were done. Therefore, the cutoff date for inclusion in the analyses of the primary efficacy outcome and the secondary efficacy outcomes was the unmasking date of each participant in both groups. The follow-up period was defined as the period (days) from the randomisation date to the unmasking date. The data lock date was March 16, 2021. Safety data in the CoronaVac intention-to-treat group were gathered in an unmasked manner after the unmasking date, and an extended safety analysis until the data lock date is also presented.

All analyses were done using SPSS for Windows (version 25.0). Descriptive analyses were presented using mean and SD for continuous variables and frequency and percentage for categorical variables. 95% CI was presented for efficacy, calculated as events per COVID-19-free person-years (ie, the sum of RT-PCR-confirmed COVID-19 cases divided by the sum of time from vaccine protection to diagnosis or unmasking).

Time to diagnosis of COVID-19 from the time of anticipated vaccine protection in both groups was presented with Kaplan-Meier survival curves. Safety analyses were done in the intention-to-treat population. Because the study product is an inactivated vaccine, a single dose was not expected to be as efficacious as two doses, and the primary efficacy analysis was therefore done in the per protocol population (defined as participants who received two doses of vaccine or placebo in accordance with group allocation). To compare adverse events between the study groups, the χ^2 test was used when the χ^2 condition was met; otherwise, Fisher's exact test was used. A Mantel-Haenszel test of trend was used in the analysis of the positive anti-RBD antibody results among age groups within both sexes. A log-rank test was used for the comparison of follow-up duration between the treatment groups. The independent data and safety monitoring board monitored the quality of evidence, adverse events, revisions in line with the current literature, individual privacy, and data reliability from the planning stage to the end of the study.

This study is registered with ClinicalTrials.gov (NCT04582344).

Role of the funding source

The Health Institutes of Turkey (TUSEB) provided the funding for this study; approved the final protocol, final manuscript, and the decision to submit for publication, but had no role in data collection, data analysis, data interpretation, or writing of the report.

Omega-CRO (Ankara, Turkey) acted as the contract research organisation representing TUSEB and contributed to correspondence between investigators, the ethics committee, and the Ministry of Health; monitoring, site management, storage, and distribution of the consumables; developing electronic case report forms, the interactive web response system, and the interactive voice response system; and data management, statistical analyses, and overall project management. Sinovac Life Sciences provided the investigational products and reviewed the data and final manuscript before submission; however, the authors retained editorial control.

Results

11 303 volunteers were screened for eligibility, and 10 218 were randomly allocated (6650 [65.1%] to the vaccine group and 3568 [34.9%] to the placebo group) between Sept 15, 2020, and Jan 6, 2021 (figure 1). After administration of the first dose and before receiving the second dose, 87 participants in the study group and 98 in the placebo group were excluded. After receiving two doses,

	Vaccine group (n=6646)	Placebo group (n=3568)
Age, years		
Median (IQR)	45 (37–51)	45 (37–51)
18–44	3259 (49.0%)	1764 (49.4%)
45–59	3387 (51.0%)	1804 (50.6%)
Sex		
Female	2831 (42.6%)	1476 (41.4%)
Male	3815 (57.4%)	2092 (58.6%)
Body-mass index*, kg/m ²		
Median (IQR)	25.7 (23.2–28.4)	25.7 (23.2–28.4)
<25	2592 (42.5%)	1372 (41.9%)
25–30	2536 (41.6%)	1414 (43.1%)
≥30	971 (15.9%)	492 (15.0%)
Study cohort†		
K1	458 (6.9%)	461 (12.9%)
K2	6188 (93.1%)	3107 (87.1%)
Health-care worker	2297 (34.6%)	1378 (38.6%)
Comorbidities present‡		
Hypertension	483 (11.8%)	249 (11.6%)
Cardiovascular disease other than hypertension	104 (2.6%)	46 (2.1%)
Chronic respiratory disease	118 (2.9%)	63 (2.9%)
Diabetes	199 (4.9%)	97 (4.5%)
Malignancy	36 (0.9%)	14 (0.7%)
Autoimmune or autoinflammatory disease	34 (0.8%)	23 (1.1%)

Data are median (IQR) or n (%). *Data were available for 6099 participants in the vaccine group and 3278 in the placebo group. †919 health-care workers were enrolled into the K1 cohort (1:1 vaccine-to-placebo randomisation ratio), of whom 667 were enrolled before Nov 18, 2020, at which point an interim safety analysis without unmasking revealed that the vaccine had a good safety profile and K2 was initiated; 252 volunteers were further recruited into K1 until Jan 4, 2021, after which the enrolment was solely into K2 (2:1 vaccine-to-placebo randomisation ratio).

‡Data were available for 4076 participants in the vaccine group and 2141 in the placebo group; participants with a medical history of malignancy or autoimmune or autoinflammatory disease did not have active disease at the time of enrolment and were not on immunosuppressive treatment.

Table: Characteristics of study participants

four (0.1%) participants in the vaccine group were excluded from all analyses because of protocol deviations (being older than 59 years on the day of randomisation). Finally, 10 214 participants (6646 [65.1%] assigned to the vaccine group and 3568 [34.9%] assigned to the placebo group) formed the intention-to-treat population, and 10 029 participants who received two doses of CoronaVac (6559 [65.4%] participants) or placebo (3470 [34.6%] participants) formed the per protocol population. On the date of data cutoff, 10 214 participants in the intention-to-treat population had reached a median 90 days (IQR 82–102) of follow-up after the first dose. All

recruitment, randomisation, and follow-up procedures were completed in 24 study centres (appendix p 8).

The main characteristics of the participants are shown in the table. The median age of the participants was 45 years (IQR 37–51), and 5191 (50.8%) were older than 45 years. 5907 (57.8%) participants were male, 4307 (42.2%) were female, 3675 (36.0%) were health-care workers, and 1463 (15.6%) were obese (body mass index ≥ 30 kg/m²). Among 6217 participants with comorbidity data reported, hypertension was the most prevalent condition (732 [11.8%] participants).

150 cases of COVID-19 were observed among 10 214 participants from the date of randomisation to the date of unmasking (median follow-up 43 days [IQR 36–48], incidence rate 122.5 cases [95% CI 104.7–142.2] per 1000 person-years). In the per protocol population (n=10 029), 41 cases of symptomatic COVID-19 occurred at least 14 days after the second dose of vaccine or placebo (91.1 cases [66.2–121.6] per 1000 person-years). Of these cases, nine were reported in the vaccine group (n=6559; 31.7 cases [14.6–59.3] per 1000 person-years) and 32 in the placebo group (n=3470; 192.3 cases [135.7–261.1] per 1000 person-years), yielding a vaccine efficacy of 83.5% (95% CI 65.4–92.1; $p < 0.0001$) for the prevention of PCR-confirmed symptomatic COVID-19.

Cumulative incidences of COVID-19-related events in the vaccine and placebo groups are shown in figure 2. There were no fatal cases of COVID-19. Hospitalisation was recorded in none of the participants in the vaccine group and six in the placebo group (36.4 hospitalisations [13.5–77.5] per 1000 person-years), giving a vaccine efficacy of 100% (20.4–100.0; $p = 0.0344$) for the prevention of COVID-19-related hospitalisation. The distribution of COVID-19 cases with regard to the WHO Clinical Progression Scale is given in the appendix (p 9). 20 PCR-confirmed symptomatic COVID-19 cases occurred between days 14 and 27 after the first dose in both groups (efficacy 46.4% [0.4–71.2], $p = 0.0486$).

1413 participants (981 in the vaccine group and 432 in the placebo group) were involved in the immunogenicity analyses. 880 (89.7%) vaccine recipients and 19 (4.4%) placebo recipients were seropositive for RBD-specific total antibody ($p < 0.0001$; figure 3). Seropositivity decreased with increasing age in women ($p_{\text{trend}} = 0.0003$) and men ($p_{\text{trend}} = 0.0084$). Virus neutralisation assays in selected samples (n=387) from seropositive participants in the vaccine group showed SN_{50} s of at least 1/15 in 356 (92.0%) of the tested samples (figure 4).

Analyses of adverse events were done in the intention-to-treat population, which excluded four participants who had protocol deviations (n=10 214; figure 1). The vaccine showed a satisfactory safety profile, with no grade 4 adverse events or deaths during the study period. Six (0.1%) of 6646 participants in the vaccine group and one (<0.1%) of 3568 in the placebo group were withdrawn from the study because of adverse events. 3845 adverse events were

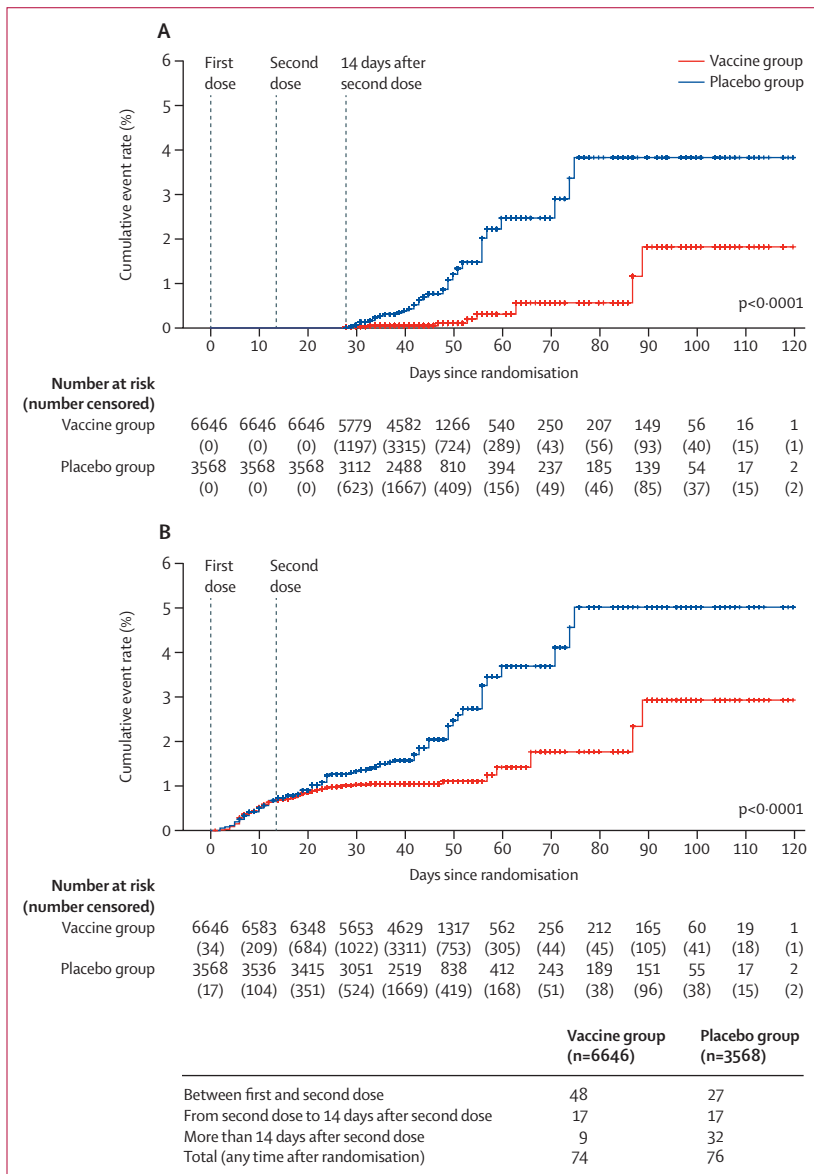


Figure 2: Cumulative incidence curves for COVID-19 cases (A) Cumulative incidence of COVID-19 in the per protocol population (assessed by analysing cases occurring 14 days or more after the second dose of vaccination). (B) Cumulative incidence of COVID-19 in the intention-to-treat population (starting immediately after randomisation).

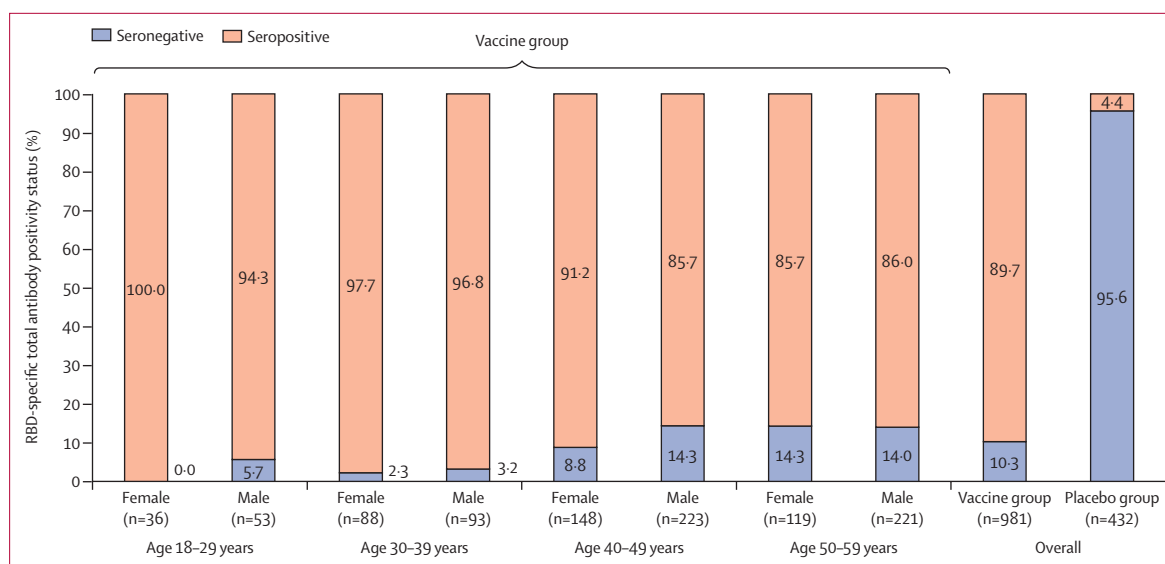


Figure 3: Seropositivity of RBD-specific total antibodies in the vaccine and placebo groups 14 days after the second dose, by age and sex

The participants with positive RBD-specific antibodies in the placebo group neither reported any symptoms during the follow-up nor had a laboratory confirmed diagnosis of COVID-19, probably representing cases with asymptomatic SARS-CoV-2 infection. RBD=receptor-binding domain.

reported among 1862 participants (1259 [18.9%] in the vaccine group and 603 [16.9%] in the placebo group, $p=0.0108$; figure 5A). Adverse events resolved in a median of 1 day (IQR 0–2). 3242 (84.3%) of 3845 adverse events were solicited (predefined) events, and were higher in the vaccine group (1148 [17.3%] participants) than in the placebo group (537 [15.1%], $p=0.0039$). Unsolicited (non-predefined) adverse events had a low incidence in both groups (figure 5A). Among all adverse events, 3469 (90.2%) were grade 1 and 3365 (87.5%) occurred within 7 days after injection. A comprehensive breakdown of adverse events is provided in the appendix (pp 10–14).

Local reactions were more commonly reported in vaccine recipients (180 [2.7%] participants) than in placebo recipients (52 [1.5%], $p<0.0001$). The most common solicited local reaction was inoculation site pain, which occurred significantly more frequently in the vaccine group (157 [2.4%] participants) than in the placebo group (40 [1.1%], $p<0.0001$). Other local adverse events, including erythema, paraesthesia, and swelling, were rare and did not differ significantly in incidence between groups (figure 5B).

The frequency of systemic adverse events was significantly higher in the vaccine group (1179 [17.7%] participants) than in the placebo group (571 [16.0%], $p=0.0263$). Events reported more frequently in the vaccine group than in the placebo group included fatigue (546 [8.2%] in the vaccine group vs 248 [7.0%] in the placebo group, $p=0.0228$), myalgia (267 [4.0%] vs 106 [3.0%], $p=0.0071$), chill (164 [2.5%] vs 63 [1.8%], $p=0.0217$), and nausea (46 [0.7%] vs 7 [0.2%], $p=0.0008$; figure 5C).

11 (0.1%) participants had serious adverse events during the study period (six [0.1%] in the vaccine group

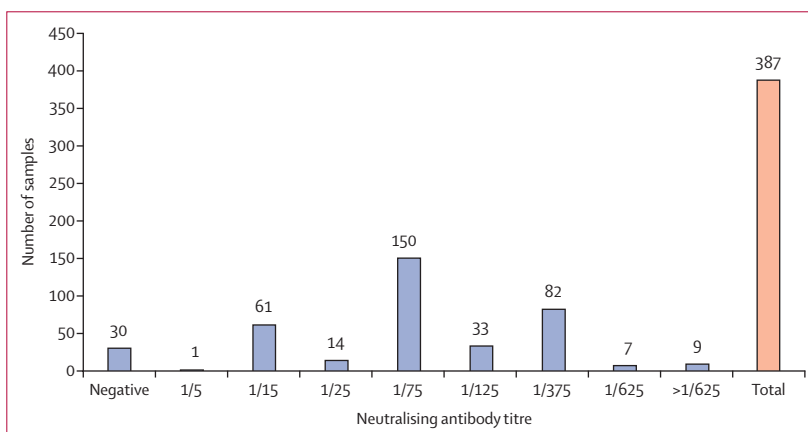


Figure 4: Neutralising antibody titres among the subset of participants included in the immunogenicity analysis

and five [0.1%] in the placebo group; appendix pp 10–14). Initially, two serious adverse events in the vaccine group were reported to have a causal relationship with the vaccine. The first participant had a grade 3 systemic allergic reaction that occurred more than 24 h after the administration of the first dose of vaccine and resolved uneventfully in the following 24 h. The other participant presented with seizure 43 days after the second dose of the vaccine; however, after an extensive work-up, this patient was diagnosed with an infiltrative glial neoplasm and, in the final assessment, this adverse event was judged to be unrelated to the vaccine.

Discussion

This interim analysis indicated that, in a population aged 18–59 years, CoronaVac had high efficacy for preventing

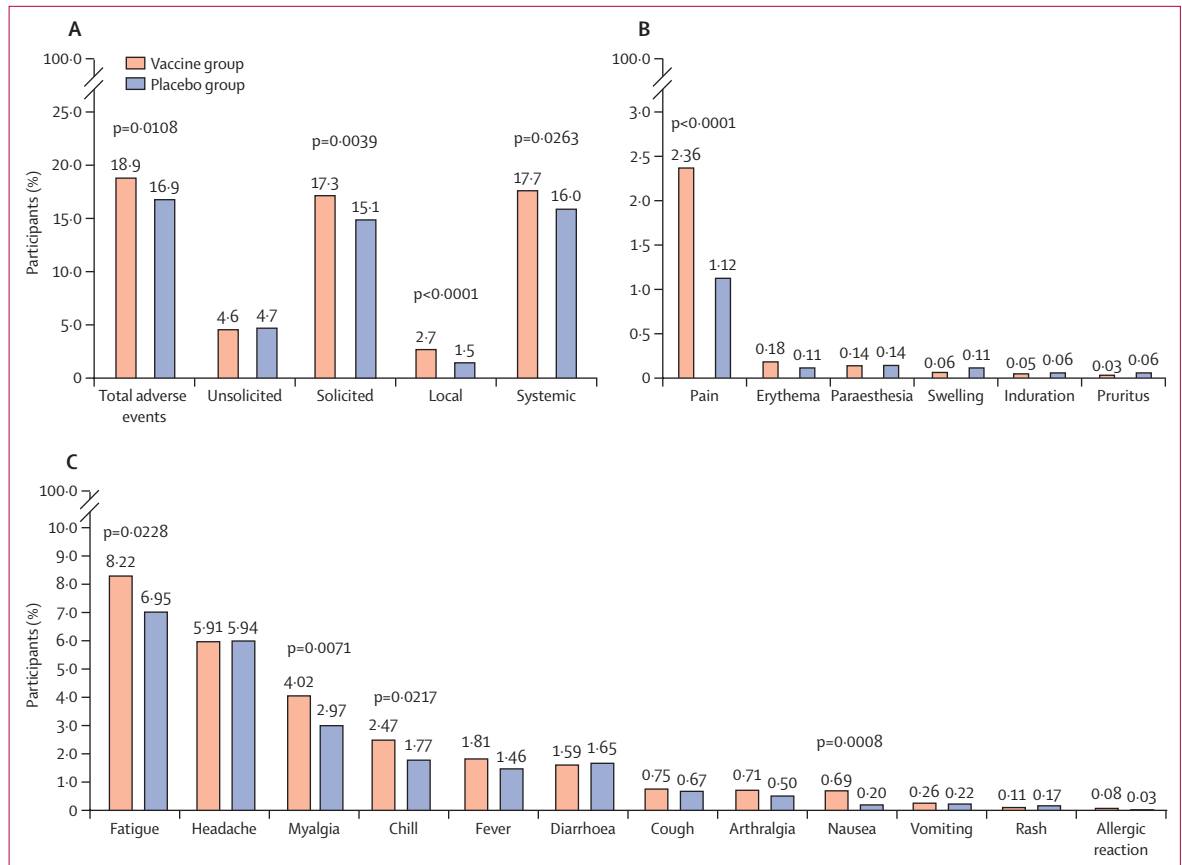


Figure 5: Adverse events

(A) Overall adverse events. (B) Local adverse events. (C) Systemic adverse events. p values are shown only for significant differences. See appendix (pp 10–12) for full data.

symptomatic COVID-19 (83.5% relative to placebo) and COVID-19-related hospitalisation (100%) at least 14 days after the second dose. Efficacy in subgroups was not a secondary outcome and the trial was not designed or powered to analyse the efficacy of the vaccine with regard to demographic variables and risk factors. Such analyses will require further trials designed accordingly. Anti-RBD antibodies developed in 89.7% of volunteers in a subset of our study sample, and 92.0% of those who were seropositive also produced protective levels of neutralising antibodies at least 14 days after the second dose of vaccine.

Inactivated SARS-CoV-2 vaccine candidates have shown promising results in preclinical trials.^{13–15} Gao and colleagues¹³ showed that, in mice, rats, and rhesus monkeys, 6 µg CoronaVac induced SARS-CoV-2-specific neutralising antibodies that effectively neutralised ten representative SARS-CoV-2 strains and provided complete protection against SARS-CoV-2 challenge in non-human primates. BBV152 (manufactured by Bharat Biotech), another inactivated vaccine, generated a quick and robust immune response with no histopathological changes in the lungs upon SARS-CoV-2 challenge in animal studies, provided adequate protection against

SARS-CoV-2 infection in rhesus monkeys, induced T-helper-1 cell-skewed immune responses with elevated IgG2a/IgG1 ratios, and increased levels of SARS-CoV-2-specific IFNγ⁺CD4⁺ T-lymphocyte responses.^{15,16} A phase 1 trial also revealed moderate seroconversion rates that persisted for up to 3 months after the second dose.^{17,18} The immune response elucidated with inactivated vaccines is not confined just to the spike protein but rather to other SARS-CoV-2 proteins—the matrix proteins, envelope proteins, and nucleoprotein—which theoretically could be reflected as a vast array of immunogenic responses.^{6,7} Voss and colleagues¹⁹ showed that, in people previously infected with SARS-CoV-2, the plasma IgG response against SARS-CoV-2 was oligoclonal and more than 80% of spike protein IgG antibodies were directed towards non-RBD epitopes in the spike protein. This finding indicates that non-RBD-directed antibodies might have a role in protection against SARS-CoV-2 infection.

Phase 1/2 trials of CoronaVac in volunteers aged 18–59 years and older than 60 years showed that the vaccine doses and schedules investigated (3 µg or 6 µg, applied 14 days or 28 days apart) all had similar safety and immunogenicity profiles.^{20,21} Considering the production

capacity and emergent need for vaccines, the 3 µg dose of CoronaVac has been suggested for efficacy assessment.²⁰ Palacios and colleagues²² reported an overall efficacy of CoronaVac against symptomatic COVID-19 of 50.7% (95% CI 36.0–62.0) 14 days or more after the second dose; however, the efficacy in preventing the need for assistance (defined as a score ≥ 3 on the WHO Clinical Progression Scale) was 83.7% (58.0–93.7) and efficacy against moderate and severe cases was 100% (56.4–100.0). In a subset of participants, neutralising antibody assays showed that there were no significant differences in the frequency of seroconversion or geometric mean titres of neutralising antibodies against the B.1.128 variant compared with those against the P.1 and P.2 variants. The study cohort only included health-care workers actively working with COVID-19 patients, and a PCR-positive case with local symptoms (such as sore throat, nasal congestion, or rhinorrhoea) was considered as a failure of the vaccine, thus indicating that the vaccine might confer lower protection against asymptomatic or mildly symptomatic cases. The interim report of the phase 3 trial in Chile with a subset of 434 health-care workers, including those aged 60 years or older, revealed high seroconversion rates for specific anti-S1-RBD IgG and neutralising antibodies, along with a robust T-cell response.²³ The interim phase 3 results of other COVID-19 vaccines have shown efficacies ranging from 62.1% to 95%.^{24–28} Higher and more rapidly established efficacies were observed with mRNA-based vaccines.^{25,26} Considering the immunogenic mechanisms of inactivated vaccines, because one dose is not expected to be as efficacious as two doses, we did not expect to and could not show an early protective effect after the first dose, in contrast to findings with mRNA vaccines.

The tolerability of CoronaVac in this study was excellent and the incidence of adverse events, most of which were solicited systemic events, was low. The majority of the adverse events were grade 1 and occurred within 7 days after the injection. No grade 4 adverse events were observed and there was only one adverse event (an allergic reaction) that required hospitalisation.

The targeted sample size could not be reached because CoronaVac was granted emergency use authorisation by the Turkish Ministry of Health while the study recruitment was ongoing, and an immediate vaccination programme was initiated for health-care workers and later for the general public in Turkey. To comply with ethical standards, recruitment was closed earlier than planned and the placebo recipients were offered vaccines, depending on their vaccination priority.

The strengths of this study include the low dropout rate, reflecting the good tolerability of the vaccine. Additionally, the participants were from different risk groups and occupations, rendering the results of the study more generalisable to the real-world context. Additionally, active symptom surveillance was pursued to detect COVID-19 cases.

This study also has several limitations. First, the median follow-up period after randomisation to the date of unmasking was 43 days (IQR 36–48), which is a very short duration of follow-up. It is not possible to comment on the long-term protective effects of the two-dose immunisation schedule with this interim analysis.

Second, one should bear in mind that the study population consisted of relatively young (median age 45 years [37–51]) and healthy individuals with a low prevalence of chronic diseases, and the overall event rate was very low. Therefore, the generalisability of the findings of this interim analysis needs to be evaluated cautiously. In particular, the number of patients hospitalised with COVID-19 was quite low and the study population consisted of individuals at relatively low risk of severe or critical COVID-19, restricting our ability to make generalised conclusions about severe disease.

Third, the study used a 14-day interval immunisation scheme, whereas the community immunisation was with a 28-day interval. It has been claimed that, although 28-day immunisation schemes elucidated better immunogenicity after the second dose, longer intervals between the two doses are correlated with a higher probability of contracting COVID-19 before getting fully immunised and a great chance of emergence of mutant variants that can replicate in the setting of suboptimal levels of neutralising antibodies.²⁹ As our results pertain to the data before the emergence of variants of concern, we cannot comment on the efficacy of CoronaVac on the prevention of infection with mutant viruses. Although one of the prespecified outcomes was seroconversion, we have avoided using this term in our reporting of the results because the immunoassay we used was a semiquantitative assay. In fact, all of the participants were seronegative at the time of screening; therefore, the seropositivity 14 days after the second dose of vaccine would indicate seroconversion. However, we could not exclude the possibility that some samples with antibody levels below a sample-to-cutoff ratio of 1 might have very low concentrations of established antibodies. The current report neither involves data on the sequential serum neutralising antibody titres nor the magnitude of T-cell responses or the duration of protectivity. However, a study setting has been established to analyse the proliferation and functional capacity of CD4⁺ and CD8⁺ T cells, and the results of an initial study in a group of COVID-19 survivors have been reported by Tavukcuoglu and colleagues.³⁰ This setting is now being used to analyse the samples from selected participants of this trial to show the functional capacity of T cells induced by CoronaVac to reinvigorate antiviral immunity against SARS-CoV-2.

In summary, our results show that CoronaVac has good efficacy against symptomatic SARS-CoV-2 infection and severe COVID-19 (ie, that requiring hospitalisation), along with a very good safety profile in a population aged 18–59 years. Because this analysis included a very short

follow-up period before the emergence of viral variants and included a young and low-risk population, further data are needed on the performance of CoronaVac to demonstrate the efficacy of the vaccine against the variants of concern and the duration of protection, and to assess the safety and efficacy in older adult populations, adolescents, and children, and individuals with specific chronic diseases.

Contributors

The principal investigators, SU and MA, conceptualised and coordinated the study. SU, MA, MDT, and HLD drafted the manuscript. SU, MA, MDT, and HLD accessed and verified the data and contributed to the analysis and interpretation of the data. SU, MA, MDT, and HLD edited the manuscript. All authors were involved in organisation, coordination, conduct, and technical support of the study; collected data; critically reviewed the manuscript and approved the final version; had full access to all data in the studies, and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Anonymous participant data will be available upon completion of the clinical trial and publication of the completed study results upon request to the corresponding author. Proposals will be reviewed and approved by the sponsor, researchers, and staff, on the basis of scientific merit and absence of competing interests. Once the proposal has been approved, data can be transferred through a secure online platform after signing a data access agreement and a confidentiality agreement.

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