Immunogenicity and safety of a severe acute respiratory syndrome coronavirus 2 inactivated vaccine in healthy adults: randomized, double-blind, and placebo-controlled phase 1 and phase 2 clinical trials

Hong-Xing Pan[1], Jian-Kai Liu[2], Bao-Ying Huang[3], Gui-Fan Li[4], Xian-Yun Chang[4], Ya-Fei Liu[4], Wen-Ling Wang[3], Kai Chu[1], Jia-Lei Hu[1], Jing-Xin Li[1], Dan-Dan Zhu[5], Jing-Liang Wu[5], Xiao-Yu Xu[6], Li Zhang[7], Meng Wang[7], Wen-Jie Tan[3], Wei-Jin Huang[7], Feng-Cai Zhu[1,8]

[1]NHC Key Laboratory of Enteric Pathogenic Microbiology (Jiangsu Provincial Center for Disease Control and Prevention), Nanjing, Jiangsu 210009, China;
[2]Shenzhen Kangtai Biological Products Co., Ltd., Shenzhen, Guangdong 518057, China;
[3]NHC Key Laboratory of Biosafety, National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China;
[4]Beijing Minhai Biological Technology Co., Ltd., Beijing 102600, China;
[5]Huaiyin District Center for Disease Control and Prevention, Huai'an, Jiangsu 223003, China;
[6]Vazyme Biotech Co., Ltd, Nanjing, Jiangsu 210000, China;
[7]National Institutes for Food and Drug Control, Beijing 102629, China;
[8]Center for Global Health, Nanjing Medical University, Nanjing, Jiangsu 211166, China.

Abstract

Background: The significant morbidity and mortality resulted from the infection of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) call for urgent development of effective and safe vaccines. We report the immunogenicity and safety of an inactivated SARS-CoV-2 vaccine, KCONVAC, in healthy adults.

Methods: Phase 1 and phase 2 randomized, double-blind, and placebo-controlled trials of KCONVAC were conducted in healthy Chinese adults aged 18 to 59 years. The participants in the phase 1 trial were randomized to receive two doses, one each on Days 0 and 14, of either KCONVAC (5 or 10 μg/dose) or placebo. The participants in the phase 2 trial were randomized to receive either KCONVAC (at 5 or 10 μg/dose) or placebo on Days 0 and 14 (0/14 regimen) or Days 0 and 28 (0/28 regimen). In the phase 1 trial, the primary safety endpoint was the proportion of participants experiencing adverse reactions/events within 28 days following the administration of each dose. In the phase 2 trial, the primary immunogenicity endpoints were neutralization antibody seroconversion and titer and anti-receptor-binding domain immunoglobulin G seroconversion at 28 days after the second dose.

Results: In the phase 1 trial, 60 participants were enrolled and received at least one dose of 5-μg vaccine ($n = 24$), 10-μg vaccine ($n = 24$), or placebo ($n = 12$). In the phase 2 trial, 500 participants were enrolled and received at least one dose of 5-μg vaccine ($n = 100$ for 0/14 or 0/28 regimens), 10-μg vaccine ($n = 100$ for each regimen), or placebo ($n = 50$ for each regimen). In the phase 1 trial, 13 (54%), 11 (46%), and seven (7/12) participants reported at least one adverse event (AE) after receiving 5-, 10-μg vaccine, or placebo, respectively. In the phase 2 trial, 16 (16%), 19 (19%), and nine (18%) 0/14-regimen participants reported at least one AE after receiving 5-, 10-μg vaccine, or placebo, respectively. Similar AE incidences were observed in the three 0/28-regimen treatment groups. No AEs with an intensity of grade 3+ were reported, expect for one vaccine-unrelated serious AE (foot fracture) reported in the phase 1 trial. KCONVAC induced significant antibody responses; 0/28 regimen showed a higher immune responses than that did 0/14 regimen after receiving two vaccine doses.

Conclusions: Both doses of KCONVAC are well tolerated and able to induce robust immune responses in healthy adults. These results support testing 5-μg vaccine in the 0/28 regimen in an upcoming phase 3 efficacy trial.

Trial Registration: http://www.chictr.org.cn/index.aspx (No. ChiCTR2000038804, http://www.chictr.org.cn/showproj.aspx?proj=62350; No. ChiCTR2000039462, http://www.chictr.org.cn/showproj.aspx?proj=63353).

Keywords: Immunogenicity; Safety; SARS-CoV-2; Inactivated vaccine; Neutralizing antibody

Introduction

The emergent virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a pandemic of

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Hong-Xing Pan, Jian-Kai Liu, Bao-Ying Huang, and Gui-Fan Li contributed equally to this work.

Correspondence to: Dr. Wen-Jie Tan, NHC Key Laboratory of Biosafety, National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China
E-Mail: tanwj@ivdc.chinacdc.cn
Dr. Wei-Jin Huang, National Institutes for Food and Drug Control, Beijing 102629, China
E-Mail: huangweijin@nifdc.org.cn
Dr. Feng-Cai Zhu, NHC Key Laboratory of Enteric Pathogenic Microbiology (Jiangsu Provincial Center for Disease Control and Prevention), Nanjing, Jiangsu 210009, China; Center for Global Health, Nanjing Medical University, Nanjing, Jiangsu 211166, China
E-Mail: jszfc@vip.sina.com

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coronavirus disease 2019 (COVID-19), as declared officially by the World Health Organization (WHO) on March 11, 2020.[1,2] This virus is highly transmissible. As of April 20, 2021, more than 140 million confirmed cases and 3.0 million deaths have been reported worldwide.[3] Given the significant morbidity and mortality caused by infection with this virus, there is an urgent need for effective and safe vaccines against COVID-19.

As of February 17, 2021, there are 69 SARS-CoV-2 candidate vaccines in various phases of clinical development and another 181 in preclinical development according to the WHO.[4] Various platforms or technologies have been applied to the development of these vaccines, yielding inactivated virus vaccines, adenovirus-vectored vaccines, recombinant protein-based vaccines, RNA vaccines, and DNA vaccines.[4] The safety, immunogenicity, and/or efficacy in humans have been reported for many of these vaccines, and most were found to have good immunogenicity and efficacy as well as an acceptable safety profile.[5-15]

Inactivated vaccines have been used against various infectious diseases for decades. Their long history of use confers some advantages, such as a well-documented safety record, well-developed and mature manufacturing processes, and the ability to present multiple viral proteins for immune recognition. To date, three inactivated SARS-CoV-2 vaccines manufactured by the Beijing Institute of Biological Products/Sinopharm (China), Wuhan Institute of Biological Products/Sinopharm (China), and Sinovac (China), as well as one adenovirus-vectored SARS-CoV-2 vaccine manufactured by CanSino Biologics (China) have received conditional approval for use in China. The expected enormous gap between the need for SARS-CoV-2 vaccines and the limited vaccine supply obligates the development of more vaccines.

Here, we report the preliminary analysis of immunogenicity and safety for the inactivated SARS-CoV-2 vaccine named KCONVAC (Shenzhen Kangtai Biological Products Co., Ltd. [China] and Beijing Minhai Biotechnology Co., Ltd. [China]) as determined by phase 1 and phase 2 clinical trials currently ongoing in Chinese adults.

Methods

Ethical approval

The studies were performed in accordance with the *Declaration of Helsinki* and Good Clinical Practice. The protocols and informed consents were approved by the institutional review board of Jiangsu Provincial Center for Disease Control and Prevention (JPCDC) (Nos. JSJK2020-A057-02 and JSJK2020-A058-02). Written informed consent was obtained from each participant before their screening for eligibility.

Study design and participants

Both the phase 1 and phase 2 trials of KCONVAC were randomized, double-blind, and placebo-controlled studies; they were conducted in succession by JPCDC beginning in October 2020. An independent data safety monitoring board was established before the start of the trials to provide oversight of the safety data during these studies. Eligible participants were healthy adults aged 18 to 59 years who were seronegative for anti-SARS-CoV-2 immunoglobulin M and immunoglobulin G (IgG) and negative for SARS-CoV-2 nucleic acid as confirmed by pharyngeal swab reverse transcription polymerase chain reaction. Individuals with confirmed cases, suspected cases, or asymptomatic cases of COVID-19 as referred to in the Information System of China Disease Prevention and Control were excluded. Those who had close contact with confirmed or suspected cases or had a history of travel to a foreign or domestic epidemic community within the 14 days before vaccination were also excluded. To be included, participants were required to have an axillary temperature of $\leq$37.0°C and have general good health as established by medical history, physical examination, and laboratory testing. Women who were pregnant or breastfeeding were excluded. Those with a previous SARS-CoV infection, mental disease, allergic reaction to any ingredient included in this vaccine or severe allergy to any other vaccine, congenital or acquired immune deficiency, human immunodeficiency virus infection, serious systemic disease, or other major chronic illness were also excluded. A complete list of the inclusion and exclusion criteria is provided in the protocol (http://www.jscdc.cn/jkfw/kygz/202104/t20210425_70351.html).

Randomization and masking

The vaccine strain of SARS-CoV-2 virus (19nCoV-CDC-Tan-Strain03, isolated in the Laboratory of National Institute for Viral Disease and Prevention, China Center for Disease Control, from clinical specimens obtained from SARS-CoV-2 positive patient) was cultivated in Vero cells. The harvested virus was inactivated by treatment with β-propiolactone, purified, and adsorbed to aluminum hydroxide (adjuvant). Each dose of vaccine contained 5 or 10 μg of inactivated SARS-CoV-2 virus antigen and 0.25 mg of aluminum in a 0.5-mL liquid formulation. The placebo contained the same adjuvant but no virus antigen. The experimental vaccines and placebo were labeled blindly with a randomization number on each vial as the only identifier.

In the phase 1 trial, a randomization ratio of 4:1 was used for both the 5-μg vaccine *vs*. placebo allocation and the 10-μg vaccine *vs*. placebo allocation. In the phase 2 trial, the eligible participants were first stratified by vaccination regimen and then randomized within each stratum at a ratio of 2:2:1 to receive the 5-, 10-μg vaccine, or placebo.

The randomization list was generated by an independent statistician using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA). A unique randomization number in sequence was allocated to each participant, who then received a vaccine or placebo dose labeled with the same randomization number. The individuals involved in the randomization and masking had no involvement in the rest of the trial. The participants, investigators, and staff

performing lab testing were all masked to the patients' treatment allocations.

Procedures

The phase 1 trial of KCONVAC was conducted with a dosage escalation method and completed before the initiation of the phase 2 trial. The first 30 eligible participants who enrolled for the phase 1 trial were randomized to receive either 5 μg of vaccine or placebo. The safety profile for the 7 days following administration of the first dose of 5-μg vaccine or placebo was determined for these initial participants. After concluding that the safety profile was acceptable, the remaining 30 participants for the phase 1 trial were enrolled and randomized to receive either 10 μg of vaccine or placebo. All participants who received the placebo in the phase 1 trial were combined into one group for analysis. The safety profile for the 7 days following administration of the first dose of 10-μg vaccine or placebo was assessed. After concluding that the safety profile was acceptable, the phase 2 trial was initiated. A single vaccination regimen was used in the phase 1 trial, that is, two doses were administered intramuscularly on Days 0 and 14 (0/14 regimen). Two vaccination regimens were used in the phase 2 trial: (1) the 0/14 regimen and (2) two doses administered intramuscularly on Days 0 and 28 (0/28 regimen).

Participants were observed for any immediate reaction for 30 min following the administration of each dose, and they were given diary cards to record any adverse events (AEs) that occurred within the following 7 days.[16] Any AEs that occurred from Day 8 through Day 28 after the administration of each dose were also recorded. To verify the AEs, clinic visits were required for participants on Days 3, 7, 14, and 28 (when applicable) after the administration of each dose in the phase 1 trial, and on Days 7 and 28 (when applicable) after the administration of each dose in the phase 2 trial. Telephone contacts were made by investigators on Days 3 and 14 after the administration of each dose in the phase 2 trial. Blood biochemistry, hematology, blood coagulation function, and urinalysis were tested before vaccination and 3 days after the administration of each dose in the phase 1 trial. AEs were graded in accordance with the scale issued by the National Medical Products Administration (NMPA), China in 2019.[17]

Blood samples to be used in antibody assays were collected from all the participants before vaccination and at 14 and 28 days after administration of the second dose. Binding antibody responses against the receptor-binding domain (RBD-IgG) of the SARS-CoV-2 spike glycoprotein were tested by using an enzyme-linked immunosorbent assay (ELISA) with a detection limit of 1:20. Neutralizing antibody responses were measured by using both a live SARS-CoV-2 (strain: 19nCoV-CDC-Tan-Strain03) micro cytopathogenic effect assay with a detection limit of 1:4 and a pseudovirus neutralization test (a vesicular stomatitis virus pseudovirus system expressing the spike glycoprotein) with a detection limit of 1:10.[18] Serum samples with an undetectable antibody titer were assigned the value of half the detection limit for calculation.

For a comparison with the immune responses induced by natural SARS-CoV-2 infection, 35 convalescent serum samples, which were collected 32 to 62 days after their diagnosis from patients with COVID-19 by the Hubei Provincial Center for Disease Control and Prevention (these patients had an average age of 48.8 years, and nine of them (26%) were classified as having severe cases), were tested with the micro cytopathogenic effect assay. The neutralizing titer was defined as the reciprocal of the highest sample dilution that protected at least 50% of cells from cytopathic effect from a live viral infection with 100 $TCID_{50}$ (50% tissue culture infectious dose) of SARS-CoV-2. The titers of RBD-IgG subtypes, including IgG1, IgG2, IgG3, and IgG4, and the antibody response to SARS-CoV-2 nucleoprotein were determined by ELISA on Days 0, 14, 28, and 42. The cellular response was assayed in the phase 1 trial by conducting an *ex vivo* interferon (IFN)-γ enzyme-linked immunospot (ELISpot) on Days 0, 14, and 28, and performing a serum cytokine test on Days 0, 14, 28, and 42. A positive IFNγ-ELISpot response was defined a difference in the average number of spot-forming cells (SFCs) per 200,000 peripheral blood mononuclear cells between stimulated and non-stimulated wells of greater than six, with a ratio of greater than two.

Outcomes

In the phase 1 trial, the primary endpoint for safety was the percentage of participants experiencing adverse reactions or AEs within 28 days following the administration of each vaccine dose. The secondary endpoints included the occurrence of serious AEs (SAEs) during the period from the administration of the first dose through 12 months after the second dose, abnormal changes in laboratory test results within 3 days following the administration of each dose, and seroconversion for RBD-IgG and neutralization antibody and the titers of these antibodies at 14 and 28 days after the administration of each dose as well as at 3, 6, and 12 months after administration of the second dose.

In the phase 2 trial, the primary endpoints for immunogenicity were neutralization antibody seroconversion, the titer of this antibody, and RBD-IgG seroconversion at 28 days after administration of the second dose. The secondary endpoints included the percentage of participants experiencing adverse reactions/AEs within 28 days following the administration of each dose, the occurrence of SAE during the period from administration of the first dose through 12 months after administration of the second dose, RBD-IgG titer at 28 days after the second dose, and RBD-IgG and neutralization antibody seroconversions and the titers of these antibodies at 14 days, and 3, 6, and 12 months after the second dose.

Seroconversion was defined as the development of an antibody titer of: (1) $<1:4$, $<1:30$, or $<1:20$ before vaccination and of $\geq 1:4$, $\geq 1:30$, or $\geq 1:20$ post-vaccination; or (2) $\geq 1:4$, $\geq 1:30$, or $\geq 1:20$ before vaccination and of ≥4-fold higher post-vaccination for neutralization antibody against live SARS-CoV-2, neutralization antibody against pseudovirus, or RBD-IgG, respectively.

Statistical analysis

Data were processed using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA). The sample size for the phase 1 trial was not determined on the basis of statistical power calculations; instead it was selected to be in line with the guidance issued by NMPA for a phase 1 vaccine trial. Because the immunogenicity results from the phase 1 trial were not available at the time that the phase 2 trial was designed, the sample size for the phase 2 trial was determined based on the assumption that the percentages of live virus-specific neutralization antibody seroconversion in the vaccine group and placebo group were 80% and 30%, respectively. A sample size of 100 in the vaccine group versus 50 in the placebo group would have sufficient power (>90%) to demonstrate a real difference in the percentages of live virus-specific neutralization antibody seroconversion between groups when tested with a two-sided alpha value of 0.05. Notably, this study was not designed to assess whether the 0/28 regimen was superior to the 0/14 regimen; consequently, the sample size is not adequately powered for comparisons between the two regimens.

All participants who received at least one dose were included in the safety analysis. The number and percentage of participants in each group who experienced adverse reactions or AEs are presented. The immunogenicity analysis was performed in the per-protocol subset of participants, which consists of participants who did not deviate from the eligibility criterion, received two doses, provided blood samples as scheduled, and had evaluable immunogenic data. Immunogenicity is expressed by the seroconversion percentage, geometric mean titer (GMT), and the associated 95% confidence interval (CI). The antibody titers of individuals were log-transformed to calculate the GMT per group. A χ^2 test or Fisher exact test was used to compare differences between groups for categorical data. An analysis of variance was used to test the difference between groups for log-transformed antibody titers. All analyses were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

The trial profiles are shown in Figures 1 and 2. A total of 60 participants were enrolled in the phase 1 trial, received at least one dose of 5-μg vaccine ($n = 24$), 10-μg vaccine ($n = 24$), or placebo ($n = 12$), and were included in the safety analysis. One participant (from the 5-μg vaccine group) discontinued the study and was not included in the immunogenicity analysis. A total of 500 participants were enrolled in the phase 2 trial, received at least one dose of 5-μg vaccine ($n = 100$ each for the 0/14 and 0/28 regimens), 10-μg vaccine ($n = 100$ for each regimen), or placebo ($n = 50$ for each regimen), and were included in the safety analysis. Five and four participants from the 0/14 (three in the 10-μg vaccine group, two in the placebo group) and 0/28 (two in the 5-μg vaccine group, one in the 10-μg vaccine group, and one in the placebo group) regimens, respectively, discontinued the study and were not included in the immunogenicity analysis. The average age across the treatment groups was 38.0 to 46.2 years old. Baseline characteristics were generally similar between all groups [Table 1]. The two studies are currently ongoing to continuously follow up the safety and antibody persistence as planned. This preliminary analysis presents the data collected through the cutoff of 28 days post-administration of the second dose.

In the phase 1 trial, 13 (54%), 11 (46%), and 7 (7/12) participants reported at least one AE, of whom 10 (42%), 6 (25%), and 6 (6/12) participants reported at least one vaccination-related AE after receiving a dose of 5-, 10-μg vaccine, or placebo, respectively. All the AEs were grade 1 or 2 in intensity. No AE of grade 3 or higher was reported. The most common solicited injection-site AE and systemic AE across the three treatment groups were pain and fatigue, respectively [Table 2]. One SAE (foot fracture) was reported in the 10-μg vaccine group. No participant discontinued the study owing to an AE. A total of 14 participants experienced abnormal changes in their blood biochemistry, hematology, or urinalysis after vaccination [Supplementary Table 1, http://links.lww.com/CM9/A614].

In the phase 2 trial, 16 (16%), 19 (19%), and 9 (18%) participants reported at least one AE, of whom 13 (13%), 17 (17%), and 6 (12%) participants reported at least one vaccination-related AE after receiving a dose of 5-, 10-μg vaccine, or placebo, respectively, in the 0/14 regimen. Similar incidences of AEs were observed in the three treatment groups who participated in the 0/28 regimen. All the AEs were grade 1 or 2 in intensity. No AE of grade 3 or higher was reported. As in the phase 1 trial, the most common solicited injection-site AE and systemic AE across the six treatment groups were pain and fatigue, respectively [Table 2]. No SAEs were reported, and no participants discontinued the study owing to an AE.

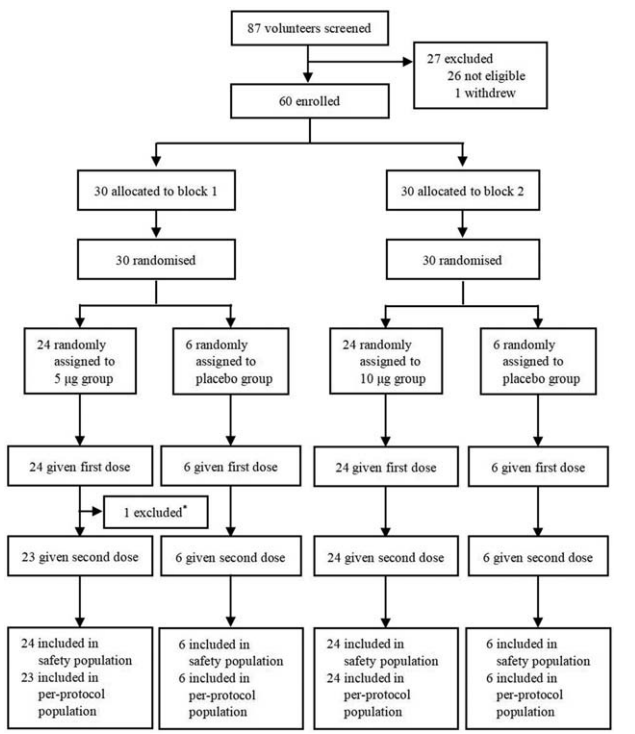

Figure 1: Study profile of the phase 1 vaccination cohort. *Excluded by investigator.

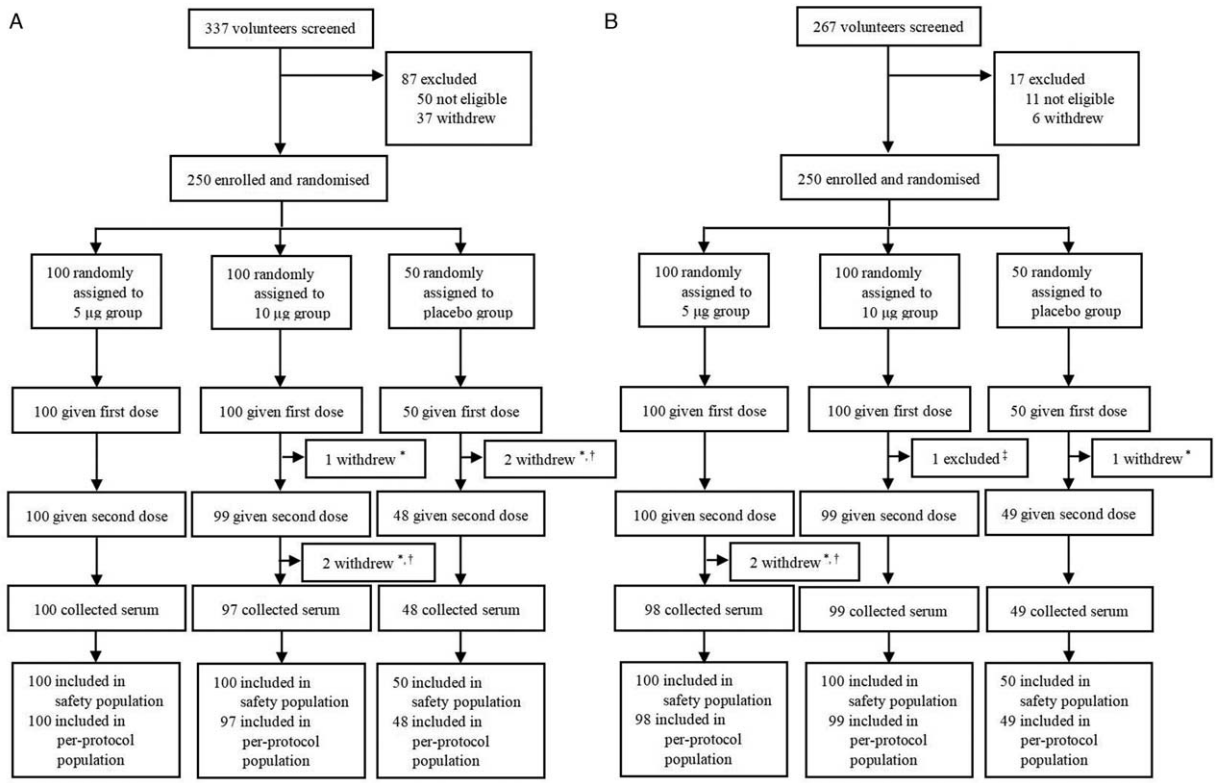

Figure 2: Study profile of the phase 2 vaccination cohort. (A) Days 0 and 14; (B) Days 0 and 28. *Participant withdrew; †Family relocation; ‡Excluded by investigator.

Table 1: Baseline characteristics of healthy Chinese adults aged 18 to 59 years participated in the phase 1 and phase 2 trials.

	Phase 1 trial (0/14)			Phase 2 trial (0/14)			Phase 2 trial (0/28)		
Items	5 μg group (*N* = 24)	10 μg group (*N* = 24)	Placebo group (*N* = 12)	5 μg group (*N* = 100)	10 μg group (*N* = 100)	Placebo group (*N* = 50)	5 μg group (*N* = 100)	10 μg group (*N* = 100)	Placebo group (*N* = 50)
Age (years), mean (SD)	38.0 (9.5)	41.0 (10.3)	38.3 (8.8)	45.5 (9.3)	44.9 (9.5)	46.2 (9.2)	42.4 (10.5)	44.5 (10.7)	41.7 (10.0)
Sex, *n* (%)									
Male	12 (50)	10 (42)	8 (8/12)	53 (53)	45 (45)	19 (38)	38 (38)	46 (46)	25 (50)
Female	12 (50)	14 (58)	4 (4/12)	47 (47)	55 (55)	31 (62)	62 (62)	54 (54)	25 (50)
Completed, *n* (%)	23 (96)	24 (100)	12 (12/12)	100 (100)	97 (97)	48 (96)	98 (98)	99 (99)	49 (98)
Discontinued, *n* (%)	1 (4)	0	0	0	3 (3)	2 (4)	2 (2)	1 (1)	1 (2)
Neutralising antibody to live SARS-CoV-2									
Seropositive	0	0	0	0	0	0	0	0	0
GMT	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)
Neutralising antibody to pseudovirus									
Seropositive	0	0	0	6 (6, 2–13)	1 (1, 0–5)	0	2 (2, 0–7)	2 (2, 0–7)	2 (4, 0–14)
GMT	8 (6–10)	10 (8–12)	7 (5–9)	8 (7–9)	8 (7–9)	7 (6–8)	11 (9–12)	9 (8–10)	9 (8–10)
RBD-IgG									
Seropositive	0	0	0	0	0	0	0	0	1 (2, 0–11)
GMT	10 (10–10)	10 (10–10)	10 (10–10)	11 (10–13)	11 (10–12)	10 (10–10)	10 (10–12)	10 (10–11)	10 (10–11)

Data are presented as *n* (95% CI [%]) for GMT, number of participants (%, 95% CI [%]) for seropositive (antibody titer ≥ detection limit). 0/14 or 0/28: Participants received two doses on Days 0 and 14 or Days 0 and 28, respectively; CI: Confidence interval. GMT: Geometric mean titer; N: Number of participants randomized into each treatment group; RBD-IgG: Antibody directed against the receptor-binding domain; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SD: Standard deviation.

The baseline serostatus in each group is summarized in Table 1. Before vaccination, the titers of neutralizing antibody directed against live virus, neutralizing antibody directed against pseudovirus, and RBD-IgG were all quite low. Almost all participants were seronegative (ie, had titers under the detection limit) for all three antibody types. The vaccine induced significant antibody responses [Table 3]. After vaccination with two doses, 88% (21/24) to 100% (24/24) of participants across the treatment groups in the phase 1 trial underwent seroconversion for

Table 2: Adverse events within 28 days following the administration of a vaccine dose.

Items	Phase 1 trial (0/14)			Phase 2 trial (0/14)			Phase 2 trial (0/28)		
	5 μg group (*N* = 24)	10 μg group (*N* = 24)	Placebo group (*N* = 12)	5 μg group (*N* = 100)	10 μg group (*N* = 100)	Placebo group (*N* = 50)	5 μg group (*N* = 100)	10 μg group (*N* = 100)	Placebo group (*N* = 50)
Any AE	13 (54)	11 (46)	7 (58)	16 (16)	19 (19)	9 (18)	25 (25)	26 (26)	11 (22)
Grade 3 or more	0	0	0	0	0	0	0	0	0
Vaccination-related AE	10 (42)	6 (25)	6 (50)	13 (13)	17 (17)	6 (12)	19 (19)	24 (24)	9 (18)
Solicited injection-site AE	4 (17)	4 (17)	2 (17)	11 (11)	8 (8)	4 (8)	16 (16)	18 (18)	7 (14)
Induration	1 (4)	0	0	2 (2)	0	0	0	3 (3)	0
Swelling	0	0	0	0	0	0	0	2 (2)	0
Erythema	2 (8)	0	0	1 (1)	0	0	1 (1)	5 (5)	0
Pain	3 (13)	4 (17)	2 (17)	8 (8)	8 (8)	4 (8)	15 (15)	12 (12)	7 (14)
Pruritus	0	0	0	2 (2)	1 (1)	1 (2)	1 (1)	2 (2)	0
Solicited systemic AE	2 (8)	1 (4)	1 (8)	6 (6)	11 (11)	4 (8)	6 (6)	10 (10)	2 (4)
Fever	0	0	0	1 (1)	2 (2)	1 (2)	1 (1)	1 (1)	1 (2)
Diarrhea	0	0	0	0	2 (2)	1 (2)	1 (1)	2 (2)	0
Inappetence	0	0	0	1 (1)	1 (1)	0	0	0	0
Vomiting	0	0	0	0	1 (1)	0	0	0	0
Nausea	0	0	0	0	0	0	0	1 (1)	0
Myalgia	1 (4)	0	0	1 (1)	1 (1)	1 (2)	1 (1)	0	0
Headache	0	0	0	2 (2)	6 (6)	0	2 (2)	0	1 (2)
Cough	0	0	1 (8)	0	3 (3)	0	1 (1)	3 (3)	0
Dyspnea	0	0	0	0	1 (1)	1 (2)	0	0	0
Skin or mucosa abnormality	0	0	0	0	1 (1)	0	0	0	0
Fatigue	2 (8)	1 (4)	1 (8)	2 (2)	6 (6)	0	2 (2)	3 (3)	1 (2)
Unsolicited AE	7 (29)	3 (13)	4 (33)	0	0	0	0	0	0

Data are *n* (%) of participants experiencing the relevant adverse events. 0/14 or 0/28: Participants received two doses on Days 0 and 14 or Days 0 and 28, respectively; AE: Adverse effect.

Table 3: Antibody responses at 14 and 28 days post-administration of the second vaccine dose.

Items	14 days post the second vaccination			28 days post the second vaccination		
	5 μg group	10 μg group	Placebo group	5 μg group	10 μg group	Placebo group
Phase 1 trial (0/14)						
N	23	24	12	23	24	12
Neutralising antibody to live SARS-CoV-2						
Seroconversion	23 (100.0, 85.2–100.0)	23 (95.8, 78.9–100.0)	0	23 (100.0, 85.2–100.0)	24 (100.0, 85.8–100.0)	0
GMT	30.9 (20.6–46.4)	40.6 (23.0–71.8)	2.0 (2.0–2.0)	29.3 (19.6–43.8)	49.1 (33.5–72.0)	2.0 (2.0–2.0)
Neutralising antibody to pseudovirus						
Seroconversion	22 (95.7, 78.1–99.9)	21 (87.5, 67.6–97.3)	0	22 (95.7, 78.1–99.9)	21 (87.5, 67.6–97.3)	0
GMT	90.4 (67.3–121.5)	116.7 (71.1–191.6)	7.8 (5.5–11.1)	69.4 (53.8–89.6)	99.8 (61.7–161.4)	7.9 (5.4–11.4)
RBD-IgG						
Seroconversion	23 (100.0, 85.2–100.0)	24 (100.0, 85.8–100.0)	0	23 (100.0, 85.2–100.0)	24 (100.0, 85.8–100.0)	0
GMT	616.0 (381.9–993.7)	1169.8 (694.2–1971.1)	10.0 (10.0–10.0)	605.3 (436.4–839.7)	962.0 (613.5–1508.6)	10.0 (10.0–10.0)
Phase 2 trial (0/14)						
N	100	98	48	100	97	48
Neutralising antibody to live SARS-CoV-2						
Seroconversion	96 (96.0, 90.1–98.9)	95 (96.9, 91.3–99.4)	0	98 (98.0, 93.0–99.8)	96 (99.0, 94.4–99.8)	0
GMT	41.5 (32.8–52.5)	48.3 (37.5–62.1)	2.0 (2.0–2.0)	37.2 (29.5–46.9)	44.5 (35.5–55.7)	2.0 (2.0–2.0)
Neutralising antibody to pseudovirus						
Seroconversion	87 (87.0, 78.8–92.9)	90 (91.8, 84.6–96.4)	0	83 (83.0, 74.2–89.8)	88 (90.7, 83.1–95.7)	0
GMT	94.4 (78.0–114.3)	118.7 (96.4–146.2)	7.7 (6.5–9.1)	74.4 (62.6–88.5)	97.6 (79.7–119.4)	8.9 (7.5–10.6)
RBD-IgG						
Seroconversion	97 (97.0, 91.5–99.4)	95 (96.9, 91.3–99.4)	2 (4.2, 0.5–14.3)	98 (98.0, 93.0–99.8)	97 (100.0, 96.3–100.0)	1 (2.1, 0.1–11.1)
GMT	636.9 (496.5–816.7)	652.7 (519.2–820.6)	11.1 (9.4–13.0)	623.0 (511.7–758.6)	686.4 (574.2–820.1)	10.5 (9.5–11.5)
Phase 2 trial (0/28)						
N	100	99	49	98	99	49
Neutralising antibody to live SARS-CoV-2						
Seroconversion	98 (98.0, 93.0–99.8)	99 (100.0, 96.3–100.0)	0	97 (99.0, 94.5–100.0)	99 (100.0, 96.3–100.0)	0
GMT	110.5 (92.4–132.2)	100.2 (84.6–118.7)	2.0 (2.0–2.0)	131.7 (109.3–158.6)	110.7 (94.7–129.4)	2.0 (2.0–2.0)
Neutralising antibody to pseudovirus						
Seroconversion	99 (99.0, 94.6–100.0)	98 (99.0, 94.5–100.0)	0	95 (96.9, 91.3–99.4)	96 (97.0, 91.4–99.4)	1 (2.0, 0.1–10.9)
GMT	276.6 (236.2–323.9)	240.1 (204.3–282.2)	8.1 (6.9–9.6)	167.4 (142.6–196.5)	153.6 (131.2–179.8)	8.6 (7.2–10.2)
RBD-IgG						
Seroconversion	98 (98.0, 93.0–100.0)	98 (99.0, 94.5–100.0)	0	96 (98.0, 92.8–99.8)	99 (100.0, 96.3–100.0)	0
GMT	2485.5 (2051.2–3011.9)	2037.3 (1643.4–2525.5)	10.2 (9.8–10.6)	1594.0 (1334.4–1904.1)	1496.8 (1255.9–1783.9)	10.3 (9.7–10.8)

Data are *n* (95% CI) for GMT, number of participants (%, 95% CI [%]) for seroconversion. 0/14 or 0/28: Participants received two doses on Days 0 and 14 or Days 0 and 28, respectively; CI: Confidence interval; GMT, geometric mean titer; N: Number of participants included in each treatment group for the per-protocol immunogenicity analysis; RBD-IgG: Antibody directed against the receptor-binding domain; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

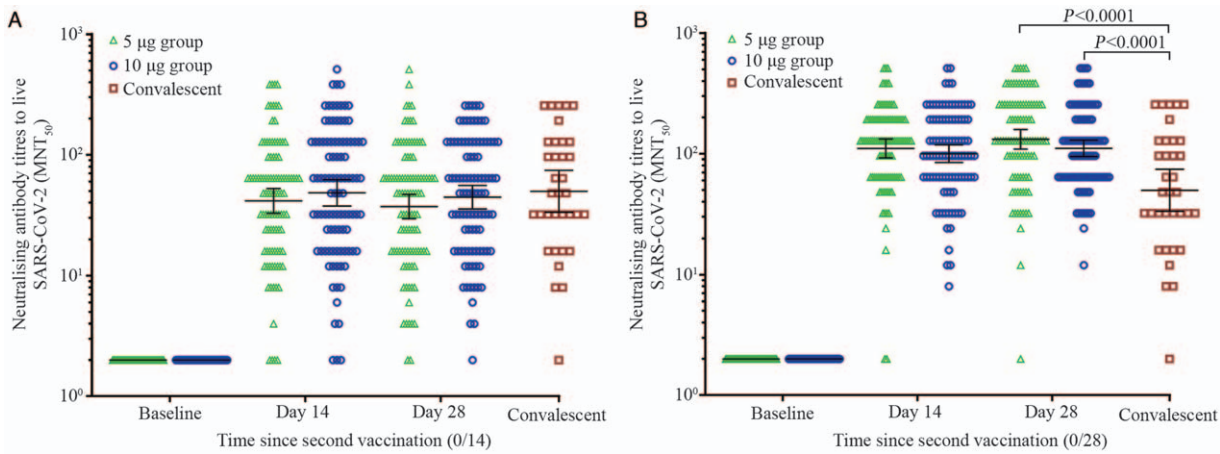

Figure 3: Neutralizing antibody titer to live SARS-CoV-2 in the phase 2 trial and convalescent sera. (A) Day 0/14 (A) or 0/28 (B) regimen. Horizontal bars show GMTs; Error bars indicate 95% CIs; and dots indicate individual antibody titers. CI: Confidence interval; GMT: Geometric mean titer; MNT_{50}: Microneutralisation test; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Table 4: Subtyping assay for RBD-IgG and titration for N-IgG in the phase 1 trial.

	Baseline			Day 28			Day 42		
Items	5 μg group (*N* = 24)	10 μg group (*N* = 24)	Placebo group (*N* = 12)	5 μg group (*N* = 23)	10 μg group (*N* = 24)	Placebo group (*N* = 12)	5 μg group (*N* = 23)	10 μg group (*N* = 23)	Placebo group (*N* = 12)
IgG1 GMT	5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.0 (5.0–5.0)	34.4 (25.2–47.0)	42.4 (30.0–59.8)	5.0 (5.0–5.0)	30.5 (25.6–37.1)	31.4 (22.5–43.9)	5.0 (5.0–5.0)
IgG2 GMT	5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.2 (4.8–5.5)	5.5 (4.6–6.5)	5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.3 (4.7–6.0)	5.0 (5.0–5.0)
IgG3 GMT	5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.8 (4.9–7.0)	6.7 (5.2–8.5)	5.0 (5.0–5.0)	5.2 (4.8–5.5)	5.8 (4.8–7.1)	5.0 (5.0–5.0)
IgG4 GMT	5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.0 (5.0–5.0)	12.0 (9.0–16.0)	17.3 (12.1–24.7)	5.0 (5.0–5.0)	9.4 (7.0–12.7)	12.7 (9.2–17.5)	5.0 (5.0–5.0)
N-IgG GMT	11.9 (7.2–19.7)	10.0 (6.7–14.9)	6.3 (4.7–8.4)	90.3 (50.4–161.7)	358.8 (208.9–616.2)	5.6 (4.7–6.7)	122.0 (72.2–206.2)	394.7 (240.6–647.8)	6.3 (4.5–8.9)

Data are GMT (95% CI). CI: Confidence interval; GMT: Geometric mean titer; N-IgG: Antibody directed against nucleoprotein; N: Number of participants included in each treatment group for the per-protocol immunogenicity analysis; RBD-IgG: Antibody directed against the receptor-binding domain.

neutralizing antibody to live virus, neutralizing antibody to pseudovirus, and RBD-IgG by 14 or 28 days post-administration of the second dose. Similar robust neutralizing and RBD-IgG antibody responses were observed in the phase 2 trial, where the vaccine induced seroconversion percentages of 83% (83/100) to 100% (99/99) across the treatment groups at 14 or 28 days post-administration of the second dose. In contrast, no placebo group participants (0/12) underwent seroconversion for any of the three antibodies in the phase 1 trial, and only two (2/48) participants in the 0/14 regimen group and one (1/49) participant in the 0/28 regimen group seroconverted in the phase 2 trial. The differences in seroconversion percentages between the vaccine groups and placebo groups for both dosages and both regimens are statistically significant ($P < 0.0001$) in both the phase 1 and phase 2 trials.

Antibody titers rose to high levels after two-dose vaccination. Across the treatment groups in the two trials, the GMTs of neutralizing antibody to live virus ranged from 29.3 to 49.1 for the 0/14 regimen group and from 100.2 to 131.7 for the 0/28 regimen group, neutralizing antibody to pseudovirus ranged from 69.4 to 118.7 for the 0/14 regimen group and from 153.6 to 276.6 for the 0/28 regimen group, and RBD-IgG ranged from 605.3 to 1169.8 for the 0/14 regimen group and from 1496.8 to 2485.5 for the 0/28 regimen group; these values are all significantly elevated from the corresponding baseline titers. Correlation coefficients are 0.65 between live-virus neutralization antibody and pseudovirus neutralization antibody, 0.66 between live-virus neutralization antibody and RBD-IgG, and 0.69 between pseudovirus neutralization antibody and RBD-IgG. The GMT of neutralizing antibody to live virus observed in convalescent serum was 49.7 (95% CI: 33.3–74.3) [Figure 3].

The RBD-IgG subtyping assay revealed that a substantial portion of RBD-IgG was IgG1, and a small part was IgG4. In contrast, only minimal amounts of IgG2 and IgG3 were detected. The RBD-IgG subtype GMT ratios (IgG1/IgG4) at 14 days after administration of the second dose were 2.8 and 2.5 in the 5- and 10-μg vaccine group, respectively. In addition, a high level of anti-nucleocapsid protein antibody (N-IgG) was detected, with GMTs ranging from 122.0 to 394.7 in the vaccine groups at 28 days after administration of the second dose [Table 4].

The vaccine induced a moderate T-cell response, with 57% (13/23) and 63% (15/24) of participants in the 5- and

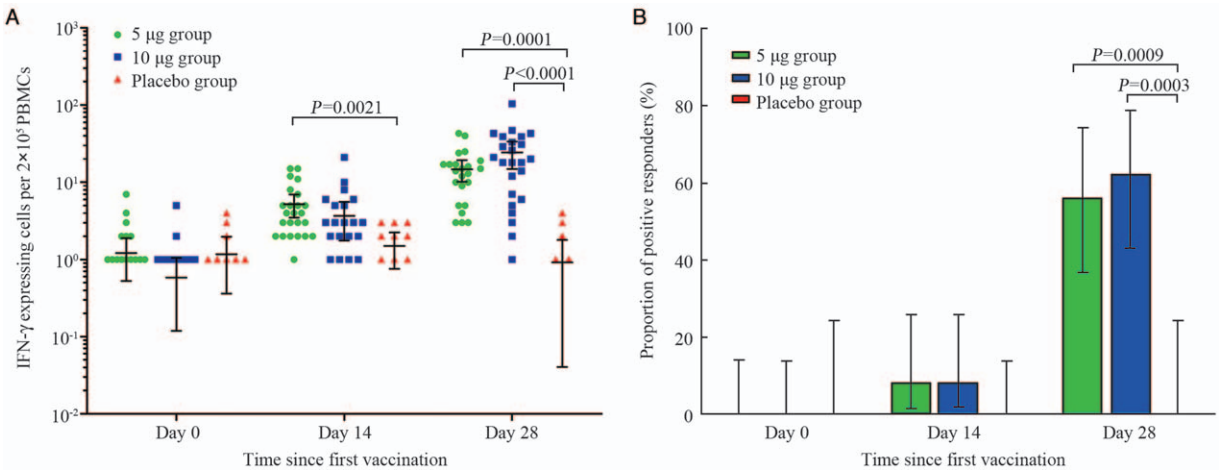

Figure 4: Specific T-cell responses measured by ELISpot in the phase 1 trial. (A) IFN-γ-positive SFCs per 200,000 cells. (B) Proportion of participants showing a positive IFN-γ-ELISpot response. ELISpot: Enzyme-linked immunospot; IFN-γ: Interferon-γ; PBMC: Peripheral blood mononuclear cell.

10-μg vaccine groups, respectively, showing positive IFNγ-ELISpot responses at 14 days after administration of the first dose in the phase 1 trial. The numbers of IFN-γ-positive SFCs per 200,000 cells were 14.8 and 24.3 in the 5- and 10-μg vaccine groups at 28 days after the first dose, respectively. In contrast, no IFNγ-ELISpot response was detected in the placebo group [Figure 4 and Supplementary Table 2, http://links.lww.com/CM9/A614]. Serum interleukin-2 (IL-2) was detected in majority of participants at 14 or 28 days after administration of the second dose. However, other serum cytokines were generally not detected [Supplementary Table 3, http://links.lww.com/CM9/A614].

Discussion

Given the urgent need for vaccines against COVID-19 and the well-documented safety record of various inactivated vaccines, we conducted the phase 1 and phase 2 trials of KCONVAC in succession to accelerate its clinical development. When the preliminary safety data for the 7 days following administration of the first dose of 5-μg vaccine in the phase 1 trial were assessed and deemed acceptable, the administration of 10-μg vaccine in the phase 1 trial was begun. The same requirement was applied when going forward from the 10-μg vaccine group of the phase 1 trial to beginning the phase 2 trial. This ensured that the studies were conducted in a dosage-escalation and scale-up manner to safeguard the safety of the participants while simultaneously accelerating the clinical process.

The preliminary safety analysis performed on the data collected after administration of the first dose through 28 days after administration of the second dose showed that KCONVAC is well tolerated in the study population. The percentages of participants who experienced an AE or vaccination-related AE among the three treatment groups of the phase 1 trial are quite similar. In the phase 2 trial, all six treatment groups had comparable percentages of participants experiencing an AE or vaccination-related AE. The injection-site AEs and systemic AEs observed in our trials are also commonly observed following the administration of other vaccines that are currently used in routine immunization practice. The safety profile of this vaccine is similar to that of other inactivated SARS-CoV-2 vaccines.[7,8] No AEs with an intensity of grade 3+ were observed in either of the two trials, expect for one vaccine-unrelated SAE (foot fracture) reported in the phase 1 trial.

The GMTs of the three antibodies assessed in the phase 2 trial are generally comparable between the two timepoints, that is, 14 or 28 days post-administration of the second dose, except that the GMTs of neutralizing antibody to pseudovirus were higher at 14 days post-administration of the second dose than those at 28 days post-administration of the second dose for both the 5-μg vaccine ($P < 0.0001$) and 10-μg vaccine ($P = 0.0001$) groups, and the GMT of RBD-IgG was higher at 14 days post-administration of the second dose than that of 28 days post-administration of the second dose for the 5-μg vaccine ($P = 0.0009$) when administered in the 0/28 regimen. This suggests that the antibody response might peak between Day 14 and Day 28 post-administration of the second dose. The antibody dynamics induced by our vaccine required further investigation. Our ongoing study will continue to monitor the persistence of the induced antibodies.

In the phase 2 trial, the 0/28 regimen induced higher GMTs compared with the 0/14 regimen, for both the 5- and 10-μg vaccine groups. At 14 days post-administration of the second dose, the GMTs induced by the 0/28 regimen are 2.0 to 3.9 times higher than the GMTs induced by the 0/14 regimen ($P < 0.0001$ for all comparisons), and at 28 days post-administration of the second dose, the GMTs induced by the 0/28 regimen are 1.6 to 3.5 times higher than the GMTs induced by the 0/14 regimen ($P \leq 0.0005$ for all comparisons). The observation that a longer interval between doses may induce a higher antibody titer is consistent with reports regarding another inactivated SARS-CoV-2 vaccine and other inactivated vaccines such as inactivated polio vaccine.[7,19] The GMT of neutralizing antibody to live virus of human convalescent serum was not significantly different from that of participants who

received the vaccine (5 or 10 μg) in the 0/14 regimen ($P \geq 0.35$ for all comparisons) but was significantly lower than that of participants who received the vaccine (5 or 10 μg) in the 0/28 regimen ($P < 0.0001$ for all comparisons).

No significant dosage-dependent antibody response was observed in the phase 1 trial or the phase 2 trial at the two timepoints, that is, 14 or 28 days post-administration of the second dose. As observed in the phase 2 trial, a longer interval between doses may induce a higher antibody titer. The impact of a longer dosing interval might mitigate, to some extent, the effect of a higher dosage.

Numerically, the GMT of RBD-IgG was higher than that of neutralizing antibodies to either the live virus or a pseudovirus, and the GMT of neutralizing antibody to pseudovirus was higher than that of neutralizing antibody to live virus when the vaccines were administered using the same regimen with the same dosage and the antibody titers were assayed at the same timepoints, which is consistent with observations from previous studies.[5,6] A correlation analysis revealed that these three antibody types are less correlated with lower coefficients than stated in previous reports. More studies are needed to explore the correlation among various antibodies to optimize antibody assay methodology.

Generally, the antibodies induced against proteins primarily belong to the IgG1 subclass, although small subsets belong to subclasses IgG3 and IgG4. Additionally, IgG3 has a short 7-day half-life.[20] This might explain why extremely low levels of IgG2 and IgG3 were detected in this study. In humans, Th1 cells are associated with generation of IgG1 and IgG3, whereas Th2 cells are associated with generation of IgG4.[21] On Days 28 and 42, the GMT of subclass IgG1 RBD-IgG was approximately three times higher than that of subclass IgG4 RBD-IgG, which might indicate a Th1-biased response. The IFNγ results from ELISpot assays provide further evidence of a Th1-biased response induced by the vaccine. IgG1 has a longer half-life as compared with other subtypes of IgG, consequently favoring antibody persistence. The serum cytokine assay detected IL-2, but not other cytokines, in a significant percentage of the participants. It is well known that cytokines play a role in inflammation. Therefore, the cytokine profile observed at 14 or 28 days after administration of a dose might have relevance to AEs, indicating if AEs might be transient.

One limitation of this preliminary analysis is that it does not include KCONVAC safety and immunogenicity data for elder adults who are at higher risk of severe COVID-19. These populations are included in our study but recruited later after the 18 to 59 adult group per protocol and so their data will be available later in our ongoing studies. The sample sizes of the present analysis are relatively small, and only physically healthy participants with no significant underlying diseases were included in the trials; therefore, any generalizations of the study results to the general population should be made with caution. Another limitation is that the study duration in the trials is relatively short, that is, 28 days post-administration of the second dose. Consequently, the long-term safety profile and antibody persistence are not in the scope of this preliminary analysis. Our ongoing studies and the upcoming phase 3 efficacy trial will be able to include these objectives. A third limitation is that we used ELISAs instead of ELISpots for testing cytokines other than IFNγ, and we collected blood samples only once between the first and second doses, so we could not get an overall profile of the cell response. The reason for using ELISAs and this minimal sampling schedule was that we intended to observe the safety only via serum cytokines because we predicted that our inactivated virus vaccine might induce a weak cellular response. A fourth limitation is that we used only a wildtype SARS-CoV-2 strain for live-virus neutralizing antibody measurement, and this strain was identical to the vaccine strain. However, several studies have reported that vaccine-induced immune responses suffer a significant decrease of neutralization potency against the B.1.1.7 variant, P.1 variant, and 501Y.V2 variant. Therefore, a partial loss of neutralization against other wildtype SARS-CoV-2 strains or variants might be expected in the serum from KCONVAC-immunized individuals, but this needs to be studied further. Finally, we used locally available convalescent serum samples as a reference in the neutralization tests but did not include standard human serum samples as recommended by the WHO. The lack of this standard reagent will make the measured neutralizing antibody titers difficult to compare with those in other studies.

In conclusion, our two trials demonstrate that KCONVAC, both at doses of 5 and 10 μg, is well tolerated and able to induce robust immune responses in adults aged 18 to 59 years. The results support testing KCONVAC at a dose of 5 μg in the 0/28 regimen in our upcoming phase 3 efficacy trial.

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Conflicts of interest

Jian-Kai Liu is an employee of Shenzhen Kangtai Biological Products Co., Ltd. Gui-Fan Li, Xian-Yun Chang, and Ya-Fei Liu are employees of Beijing Minhai Biotechnology Co., Ltd. All other authors declare that no competing interests exist. The sponsors of the studies participated in study design, and had no role in data collection, analysis,

interpretation, and manuscript writing. All authors had full access to all the data and had final responsibility for the decision to submit for publication.

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