Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Safety and immunogenicity of a bivalent SARS-CoV-2 protein booster vaccine, SCTV01C in adults previously vaccinated with inactivated vaccine: A randomized, double-blind, placebo-controlled phase 1/2 clinical trial

To the editor,

In this journal, Liu and colleagues evaluated the immunogenicity of seven COVID-19 vaccines given as third dose boosters following two doses of primary series of ChAdOx1 nCov-19 or BNT162b2.[1] However, with the emergence of the SARS-CoV-2 variants, existing evidence shows the waning protection of COVID-19 primary/booster vaccination and the reduced effectiveness of the monovalent vaccines developed based on the original SARS-CoV-2 strain against COVID-19.[2] Recent evidences indicated that multivalent booster vaccination could provide significant additional protection against symptomatic SARS-CoV-2 infection in persons who had previously received monovalent vaccine doses.[3,4] Herein, with this Phase 1/2 safety and immunogenicity clinical trial, we assessed a novel SARS-CoV-2 bivalent vaccine, SCTV01C, given as a heterologous booster for people who had previously received the primary series of an inactivated vaccine. The data showed that SCTV01C was well tolerated with reactogenicity profile that was comparable to that of inactivated vaccines, and induced substantial neutralizing antibody responses to Delta and Omicron variants.

SCTV01C is a recombinant protein vaccine composed of the spike protein extracellular domain (S-ECD) of Alpha (B.1.1.7) and Beta (B.1.351) variants, and adjuvanted with a squalene-based oil-in-water emulsion SCT-VA02B. The bivalent design increases the coverage of epitope mutations and may provide improved cross-strain protection. Preclinical studies showed that SCTV01C remained stable at 25 °C for six months and at 2–8 °C for over 24 months, and induced potent T-helper-1-biased T-cell responses and broad-spectrum neutralizing antibodies against a panel of genetically distinct lineages of SARS-CoV-2 variants, including D614G, Alpha, Beta, Delta, Gamma, Omicron, Lambda, Mu, Iota, Kappa, Epsilon, C.36.3 B1.618 and 20I/484Q.[5,6]

Between January 18, 2022, and April 5, 2022, 234 adults who had previously received primary series of BBIBP-CorV (Sinopharm inactivated vaccine) 3–24 months earlier and had no history of infections with SARS-CoV-2 were randomly assigned to receive placebo (normal saline, $n = 75$), 20 μg SCTV01C ($n = 79$) or 40 μg SCTV01C ($n = 80$) and completed at least a 4-week follow-up (Supplementary Methods). No deaths or hospitalizations, serious adverse events (SAEs) and AEs of special interest (AESIs) were reported. The overall occurrence of treatment related AE (TRAE) was 27.7%. 25.3%, 30.4%, and 25.0% participants in the placebo, 20 μg SCTV01C and 40 μg SCTV01C groups experienced at least one TRAE within 28 days. 20 μg and 40 μg SCTV01C showed similar occurrence of solicited AEs (24.1% vs. 17.5%). The most common solicited AEs with SCTV01C were injection-site pain (11.9%) and pyrexia (6.3%). There were 3 reports of Grade 3 pyrexias (1.9%) in SCTV01C groups (Table 1 and Supplementary Fig. 1). All AEs resolved within 7 days without intervention. The overall reactogenicity profile of SCTV01C was similar to that of reported primary and booster vaccination with the inactivated vaccines (CoronaVac showed 6–18% of solicited ARs and 1%−16% of injection-site pain. BBIBP-CorV showed 12.72% of solicited ARs, 3.98% of injection-site pain and 4.2% of headaches)[4,7], and also consistent with that of reported recombinant protein vaccines, NVSI-06–08[4] given as a heterologous booster primed with the BBIBP-CorV series.

Table 1
Adverse events and reactions after the booster vaccination.

AE	Saline ($N = 75$) n (%)	SCTV01C 20 μg ($N = 79$) n (%)	SCTV01C 40 μg ($N = 80$) n (%)	SCTV01C Total ($N = 159$) n (%)
TEAEs	21 (28.0)	29 (36.7)	23 (28.8)	52 (32.7)
Vaccine-related TEAEs	19 (25.3)	24 (30.4)	20 (25.0)	44 (27.7)
AEs within 0–7 days	13 (17.3)	18 (22.8)	15 (18.8)	33 (20.8)
AEs within 0–28 days	19 (25.3)	23 (29.1)	20 (25.0)	43 (27.0)
Grade 3 of above AEs	0	0	3 (3.8)	3 (1.9)
Grade 3 of Vaccine-related AEs	0	0	3 (3.8)	3 (1.9)
Solicited AEs				
Any	12 (16.0)	19 (24.1)	14 (17.5)	33 (20.8)
Grade ≥3	0	0	3 (3.8)	3 (1.9)
Solicited Local AEs				
Any	1 (1.3)	13 (16.5)	9 (11.3)	22 (13.8)
Grade ≥3	0	0	0	0
Injection site pain	1 (1.3)	10 (12.7)	9 (11.3)	19 (11.9)
Injection site pruritus	0	2 (2.5)	1 (1.3)	3 (1.9)
Injection site swelling	0	2 (2.5)	0	2 (1.3)
Injection site erythema	0	1 (1.3)	0	1 (0.6)
Solicited Systemic AEs				
Any	11 (14.7)	8 (10.1)	6 (7.5)	14 (8.8)
Grade ≥3	0	0	3 (3.8)	3 (1.9)
Pyrexia	6 (8.0)	6 (7.6)	4 (5.0)	10 (6.3)
Headache	4 (5.3)	1 (1.3)	1 (1.3)	2 (1.3)
Fatigue	0	1 (1.3)	0	1 (0.6)
Insomnia	0	0	1 (1.3)	1 (0.6)
Myalgia	2 (2.7)	1 (1.3)	0	1 (0.6)
Pruritus	1 (1.3)	1 (1.3)	0	1 (0.6)
Vaccine-related Solicited AEs	12 (16.0)	18 (22.8)	14 (17.5)	32 (20.1)
Grade ≥3	0	0	3 (3.8)	3 (1.9)
Pyrexia	0	0	3 (3.8)	3 (1.9)
Unsolicited AEs				
Any	12 (16.0)	16 (20.3)	15 (18.8)	31 (19.5)
Grade ≥3	0	0	0	0

TEAE= treatment-emergent adverse event.

Viral neutralizing antibody responses are highly predictive of immune protection from symptomatic SARS-CoV-2 and have been used to infer COVID-19 vaccine effectiveness.[8,9] In this study, the primary analyses evaluated the geometric mean concentration

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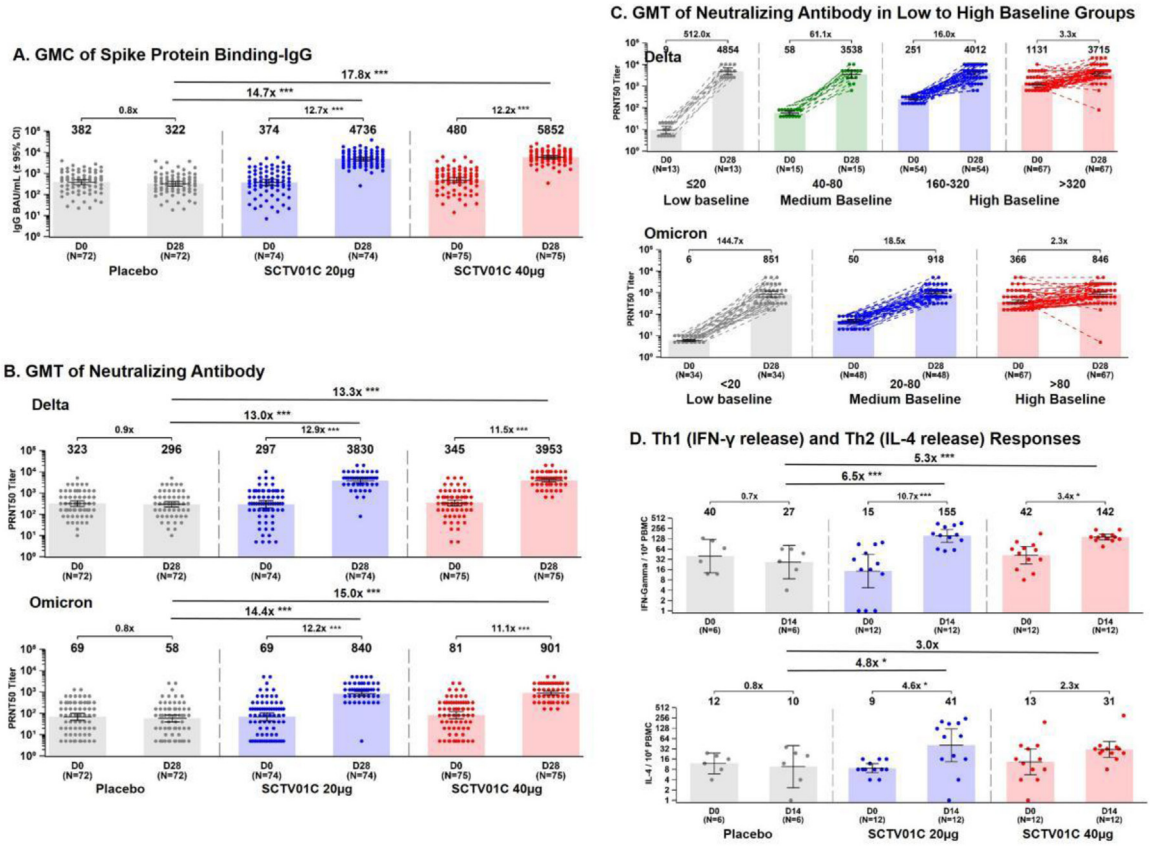

Fig. 1. **A:** GMC (BAU/mL) of anti- spike protein IgG. IgG were measured using Enzyme-linked Immunosorbent Assay (ELISA) and converted to geometric mean concentration (GMC) using WHO assigned International Binding Antibody Units (BAU); **B:** GMTs of neutralizing antibodies against live SARS-CoV-2 Delta and Omicron. GMTs were measured using 50% plaque reduction neutralization test (PRNT50); **C:** Fold increase of neutralizing antibodies with SCTV01C against live SARS-CoV-2 Delta Omicron in groups with high, medium and low baseline titers; **D:** Th1 (IFN-γ release) and Th2 (IL-4 release) responses. The peripheral blood mononuclear cells were collected before and on day 14 after booster vaccination. The number of specific T cells with secretion of IFN-γ (Th1) and IL-4 (Th2) were measured with spot per 10^6 PBMC using enzyme-linked immunospot (ELISpot) assay. Note: $^*p<0.05$; *** $p<0.0001$.

(GMC) of the specific anti-spike protein and the geometric mean titer (GMT) of neutralizing antibody against Delta (B.1.617.2) and Omicron (B.1.1.529).

At day 28 post injection, the GMCs of the specific spike binding IgG (converted to WHO International Binding Antibody Units, BAU) were 322 (95% CI: 245–424), 4736 (95% CI: 3905–5745), and 5852 (95% CI: 4942- 6930) BAU/ml, with 0.8, 12.7 and 12.2-fold over baseline (D0), for the placebo, 20 μg SCTV01C and 40 μg SCTV01C groups, respectively (Fig. 1A and Supplementary Table 1). The GMCs of SCTV01C were comparable to those of heterologous BNT162b2 booster in participants who had received primary series of inactivated vaccines (4349 BAU/ml), and higher than those of homologous prime/booster with CoronaVac (312 BAU/ml), and heterologous booster with the adenovirus vaccines (ChAdOx1: 2173 BAU/ml and Ad26.COV2: 2184 BAU/ml).[10]

The Day 28 GMTs of neutralizing antibody against live Delta variant were 296 (95% CI: 221–398), 3830 (95% CI: 3144- 4664), and 3953 (95% CI: 3364–4644), with 0.9, 12.9 and 11.5-fold over baseline, and GMTs against Omicron BA.1 were 58 (95% CI: 40–85), 840 (95% CI: 665–1060), and 901 (95% CI: 751–1081), with 0.8, 12.2 and 11.1-fold over baseline for the placebo, 20 μg SCTV01C and 40 μg SCTV01C, respectively (Fig. 1B and Supplementary Table 1). The GMT levels with SCTV01C compared favorably to those reported in the literatures (The peak GMTs against Delta and Omicron variants were 1653 (95% CI:1118–2443) and 223 (95% CI:108–458) after a booster dose of BNT162b2), although cautions should be taken in interpreting data from different labs due to significant assay variabilities. [7,10]

Post hoc analyses evaluated the impact of the pre-existing SARS-COV-2 immunity on the neutralizing antibody responses. The participants were assigned to different groups based on their baseline titers. Participants with the GMTs at baseline below the lower limit of quantitation (LLOQ: 20) was considered as low baseline titer, GMTs in the range of 1 to 4-fold over LLOQ (GMT: 20–80) were considered as medium baseline titer, and GMTs of 4-fold over LLOQ (GMT > 80) for Omicron or 8-fold over LLOQ (GMT > 160) for Delta were considered as high baseline titer. The Day 28 GMTs against Delta with SCTV01C were 4854, 3538 and 3848 with 512.0, 61.1, and 5.2-fold over baseline, and GMTs against Omicron were 851, 918 and 846 with a fold of 144.7, 18.5 and 2.3 over baseline for the low, medium and high baseline titer groups, respectively (Fig. 1C). Notably, SCTV01C elicited consistently high GMTs to Delta and Omicron, irrespective of baseline GMTs levels of the participants.

The peripheral blood mononuclear cells were collected to assess specific Th1 (IFN-γ release) and T2 (IL-4 release) responses before and 14 days after injection. The number of specific IFN-γ secreting T-cells (Th1) increased by 0.7, 10.7 ($p<0.0001$) and 3.4- ($p<0.05$) fold from the baseline, and the number of IL-4 secreting T-cells (Th2) increased by 0.8, 4.6 ($p<0.05$) and 2.3- fold from the baseline for saline, 20 μg SCTV01C and 40 μg SCTV01C, respectively (Fig. 1D and Supplementary Table 2). The results suggested that SCTV01C booster induced T-helper-1 biased CD4+*T* cell responses.

In summary, the current data showed that SCTV01C booster was safe with reactogenicity profile that was comparable to that of the inactivated vaccines, and induced consistently high neutral-

izing antibody responses to Delta and Omicron variants. SCTV01C may be a new tool against emerging variants of SARS-CoV-2.

Declaration of Competing Interests

Dr. Liangzhi Xie, Dr. Jian Li, and Dr. Yuanxin Chen are employees of Sinocelltech Ltd. and have ownership or potential stock option interests in the company. All authors declare no other conflicts of interest.

Data availability

Anonymized participant data will be made available when the trials are complete, upon requests directed to the corresponding author.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.12.003.

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