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 recombinant protein vaccine, SCTV01C in unvaccinated adults: A randomized, double-blinded, placebo-controlled, phase I clinical trial

To the editor,

In this journal, Liu and colleagues showed the potential efficacy of a recombinant protein vaccine for COVID-19 as a boost strategy.[1] However, the rapid emergence of immune-evasive SARS-CoV-2 variants, especially the Omicron sub-variants, called for development of vaccines with cross-protection to a broad-spectrum of variants. SCTV01C is a recombinant bivalent vaccine comprised of trimeric spike extracellular domain (S-ECD) of SARS-CoV-2 variants Alpha (B.1.1.7) and Beta (B.1.351), and adjuvanted with SCT-VA02B, a squalene-based oil-in-water emulsion. In preclinical studies, 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.[2,3] We have performed a dose-escalation phase 1 trial to assess the reactogenicity and immunogenicity of SCTV01C in health adults (NCT05148091). Our results showed that SCTV01C vaccination with a two-dose regimen was safe with low adverse event (AE) rates (no serious AE) and induced promising cross-neutralizing antibody titers against multiple SARS-CoV-2 variants of concern, including Delta, Omicron and its sublineages, with a near 100% seroconversion rates.

In this clinical trial, between December 8, 2021 and April 30, 2022, 307 participants were screened, of which 84 participants (52 males and 32 females) that had no previous SARS-CoV-2 vaccination and infection were enrolled to receive 20 μg SCTV01C, 40 μg SCTV01C, the adjuvant or the placebo (Supplementary Table 1, Supplementary Fig. 1 and Supplementary Methods). All participants received two injections 28 days apart, and completed 4-week follow-up after dose 2 and up to Day 118. No deaths or hospitalizations, serious adverse events (SAEs), AEs of special interest (AESIs) or medically attended AEs (MAAEs). No clinically significant changes in routine clinical laboratory values were identified. The most frequent solicited adverse reactions (ARs) of SCTV01C were Grade 1 local injection-site pain (18.3%) and fever (10%), and only Grade 3 fever was reported. All the ARs resolved within 7 days without intervention. The overall solicited ARs of SCTV01C were less in older adults than in young adults (10% vs. 45%). The 20 μg and 40 μg SCTV01C groups showed similar incidence rates of solicited ARs (27.5% vs. 30.0%), and the occurrence of solicited ARs after the second dose were similar or less than those after the first dose (15.0% vs 20.0%). The SCT-VA02B adjuvant was tolerated in terms of solicited ARs, with one report of mild injection-site pain (8.3%), and one Grade 1 fever (8.3%) (Table 1, Supplementary Fig. 2). The reactogenicity profile of SCTV01C compares favorably to the reported AEs of the authorized mRNA vaccines and adenovirus vector vaccines, which showed overall related AEs of 71.6% to 88.6%.[4,5] The injection-site pain and fever was the only SCTV01C associated AR occurred >5% subjects. However, ARs such as fatigue, headache, joint paint, myalgia, nausea, fever, chill, irritability, loss the appetites, sleepiness, and pain at the injection-site pain are commonly observed with mRNA vaccines or adenovirus vector vaccines.[4-5]

The immunogenicity assessment was performed on the day before the first vaccination (Day 0, baseline), 28 days after the first vaccination (Day 28, before the second vaccination), 42 days after the first vaccination (Day 42, 14 days after the second dose) and 56 days after the first vaccination (Day 56, 28 days after the second dose). Both first and second vaccination induced significant specific spike binding IgG and neutralizing antibody responses to SARS CoV-2 variants, and levels of the immune responses to 20 µg and 40 µg of SCTV01C were similar.

For combined 20 µg and 40 µg SCTV01C groups, Day 42 geometric mean concentration (GMC, converted to WHO assigned International Binding Antibody Units (BAU)) of specific spike binding IgG against the two antigen-matched variants (Alpha and Beta) ranged from 13,895 to 14,622 BAU/ml (Fig. 1, Supplementary Table 2), as compared to literature reported GMCs of spike binding IgG (against the vaccine-matched original SARS-CoV-2 strains), which were in a range between 64.4 and 3985 BAU/mL for inactivated vaccines, adenovirus viral vaccine, and mRNA vaccines.[6,7]

For the antigen-mismatched Delta variant, SCTV01C induced specific spike binding IgG of 5122 (95% CI: 4080–6431) BAU/ml and the geometric mean titers (GMT) of live virus neutralizing antibodies peaked at 428 (95% CI: 356 to 514) (Fig. 1A, B, Supplementary Tables 2 and 3). Contrastingly, the primary series of BNT162b2, mRNA1273 and Ad26.COV2 elicited spike binding IgG to Delta variant peaked at 1144 BAU/ml, 1123 BAU/ml and 245 BAU/ml,[8] respectively.

For the live Omicron variant, two doses of SCTV01C induced the GMTs of 63 (95% CI: 61–95) in young adults and 109 (95% CI: 69–172) in older adults (Fig. 1B, Supplementary Table 3), which was 2.5–4.3-fold of the reported GMT threshold (25.6) for 50% protection from symptomatic SARS-CoV-2 infection.[9] The GMT of live virus neutralizing antibodies increased 19-fold (95% CI: 15–24) from baseline with a seroconversion rate of 98.2% in contrast to the low seropositive rates against Omicron of most authorized COVID-19 vaccines.[6,9] Studies of the primary series of vaccination showed that the neutralizing GMTs against live Omicron variant were 20 (15% above the limit of detection) for BNT162b2, 15 (36% above the limit of detection) for mRNA-1273.[10]

The broad-spectrum immune responses after SCTV01C vaccination were supported by the seroconversion rates (defined as

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Table 1
Adverse events and reactions.

AE	Saline	Adjuvant	SCTV01C		
	($N = 12$)	($N = 12$)	18–59 yrs, 20 μg ($N = 20$)	18–59 yrs, 40 μg ($N = 20$)	≥60 yrs, 20 μg ($N = 20$)
			First Dose, n (%)		
Solicited AEs within 7 days					
Any	0	1 (8.3)	9 (45.0)	2 (10.0)	1 (5.0)
Grade ≥3	0	0	0	0	0
Solicited local ARs					
Any	0	1 (8.3)	8 (40.0)	2 (10.0)	1 (5.0)
Grade ≥3	0	0	0	0	0
Injection site erythema	0	0	1 (5.0)	0	0
Injection site induration	0	0	1 (5.0)	0	0
Injection site pain	0	1 (8.3)	8 (40.0)	2 (10.0)	0
Injection site pruritus	0	0	0	0	1 (5.0)
Injection site swelling	0	0	1 (5.0)	0	0
Solicited systemic ARs					
Any	0	0	4 (20.0)	1 (5.0)	0
Grade ≥3	0	0	0	0	0
Anxiety	0	0	1 (5.0)	0	0
Diarrhoea	0	0	1 (5.0)	0	0
Fatigue	0	0	1 (5.0)	1 (5.0)	0
Pyrexia	0	0	1 (5.0)	0	0
Somnolence	0	0	0	1 (5.0)	0
Unsolicited ARs					
Any	1 (8.3)	3 (25.0)	5 (25.0)	7 (35.0)	6 (30.0)
Grade ≥3	0	0	0	0	0
			Second Dose, n (%)		
Solicited AEs within 7 days					
Any	1 (8.3)	1 (8.3)	3 (15.0)	5 (25.0)	1 (5.0)
Grade ≥3	0	0	0	1 (5.0)	0
Solicited local ARs					
Any	0	0	3 (15.0)	1 (5.0)	0
Grade ≥3	0	0	0	0	0
Injection site erythema	0	0	1 (5.0)	0	0
Injection site induration	0	0	1 (5.0)	0	0
Injection site pain	0	0	3 (15.0)	1 (5.0)	0
Injection site swelling	0	0	0	1 (5.0)	0
Solicited systemic ARs					
Any	1 (8.3)	1 (8.3)	2 (10.0)	5 (25.0)	1 (5.0)
Grade ≥3	0	0	0	1 (5.0)	0
Cough	0	0	0	2 (10.0)	0
Diarrhoea	0	0	1 (5.0)	0	0
Myalgia	0	0	0	1 (5.0)	0
Pruritus	0	0	0	1 (5.0)	0
Pyrexia	1 (8.3)	1 (8.3)	1 (5.0)	4 (20.0)	1 (5.0)
Unsolicited ARs					
Any	3 (25.0)	4 (33.3)	6 (30.0)	9 (45.0)	5 (25.0)
Grade ≥3	0	0	0	0	0

AE = adverse event; AR = adverse reaction.

an increase in titers of at least 4-fold over baseline). A near 100% seroconversion rates of the spike protein binding IgG, pseudovirus neutralizing antibody and live virus neutralizing antibody responses to all tested variants were observed post second dose of SCTV01C. Among 60 participants who had received two doses of SCTV01C, only one older participant showed low increase (≤ 4-fold over baseline) in neutralizing antibody responses to Omicron variant. The first dose of SCTV01C (Day 28) also induced 100%, 100%, and 98.2% seroconversion rates of the specific binding IgG to Alpha, beta and Delta variants, respectively (Supplementary Table 4).

Consistent with the results of live virus neutralization assay, neutralizing antibody titers against pseudoviruses bearing the spike proteins BA.1, BA.2, BA.2.12.1 and BA.4/5 increased by 11.5, 11.1, 9.5 and 7.5-fold, respectively in adults who received 2 doses of 20 μg SCTV01C (Fig. 1C). Importantly, seroconversion rates measured by the pseudovirus neutralizing assay were 100%, 100%, 100% and 78.9% for the BA.1, BA.2, BA.2.12.1 and BA.4/5, respectively.

In summary, SCTV01C showed a clinically acceptable reactogenicity profile, and induced promising immunogenicity against the two vaccine variants, Alpha and Beta as well as cross-neutralization against Delta and Omicron variants, including the Omicron sub-variants. This is, to the best of our knowledge, the first COVID-19 candidate vaccine that showed promising activities against Omicron BA.4/5 in vaccine-naïve population with a randomized clinical trial.

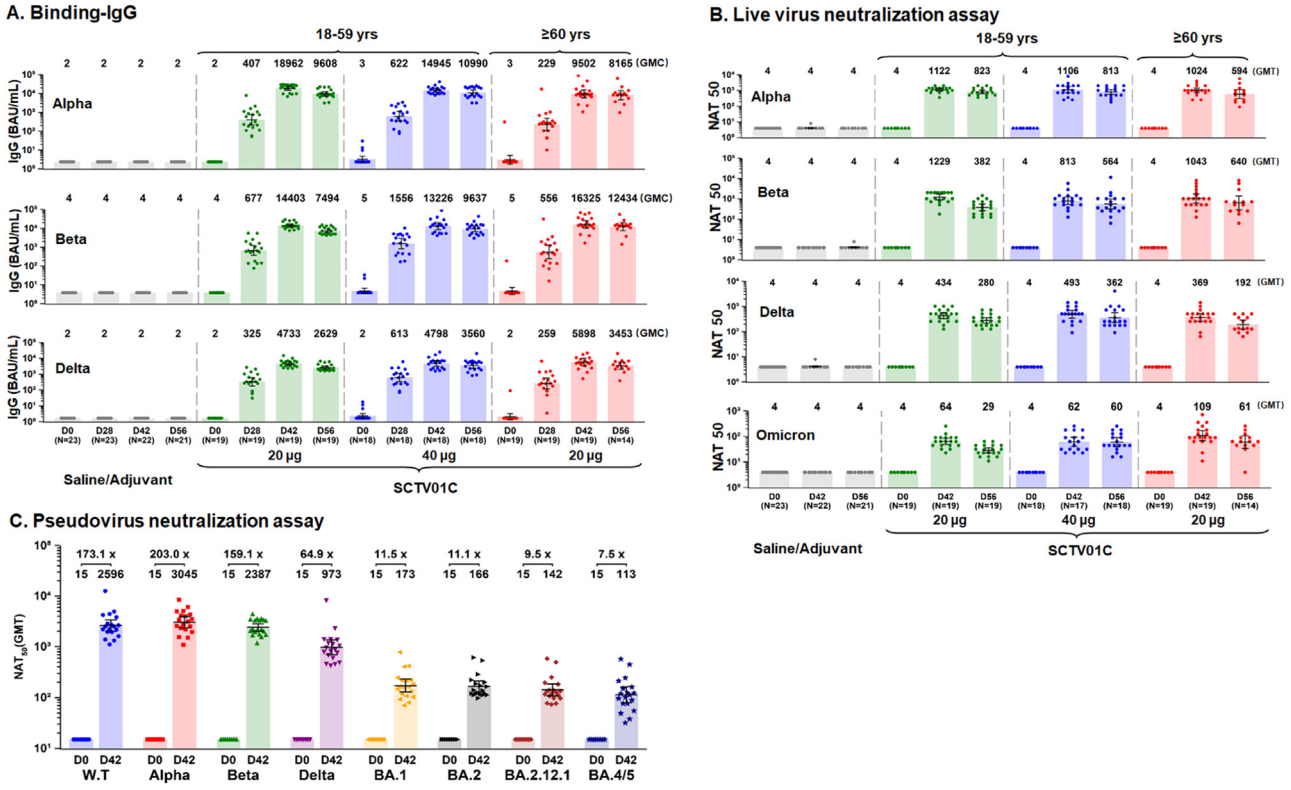

Fig. 1. A: Specific binding-IgG to the spike protein of Alpha, Beta, and Delta variants on days 0, 28, 42 and 56. IgG levels were measured using Enzyme-linked Immunosorbent Assay (ELISA) and converted to WHO assigned International Binding Antibody Units (BAU/ml, NIBSC code: 20/268); B: GMTs of neutralizing antibody responses to live SARS-CoV-2 Alpha, Beta, Delta, and Omicron variants on days 0, 42 and 56. GMTs of neutralizing antibody activities were measured using micro-neutralization assay (MN50); C: Neutralizing antibody activities to pseudotyped SARS-CoV-2 wild type, Alpha, Beta, Delta variants and Omicron sublineages BA.1, BA.2, BA.2.12.1 and BA.4/5. Sera were collected in 19 young adults who had received two dose of 20 μg SCTV01C. GMTs of neutralizing antibody activities were quantified using pseudovirus neutralization test (pVNT) on Day 0 and Day 42. Immunogenicity values that were below the lower limit of quantitation (LLOQ) were set to 0.5x LLOQ in the analysis.

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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Declaration of Competing Interest

Dr. Shuping Xu, Dr. Xinjie Yang, Yongpan Fu, and Dr. Liangzhi Xie are employees of Sinocelltech Ltd. and have ownership or potential stock option interests in the company. All authors declare no other conflicts of interest.

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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.2022.11.008.

References

1. Liu X, Munro A, Feng S, Janani L, Aley PK, Babbage G, et al. Persistence of immunogenicity after seven COVID-19 vaccines given as third dose boosters following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK: three month analyses of the COV-BOOST trial. *J Infect* 2022;**84**:795–813.
2. Wang R, Huang X, Cao T, Sun C, Luo D, Qiu H, et al. Development of a thermostable SARS-CoV-2 variant-based bivalent protein vaccine with cross-neutralizing potency against Omicron subvariants. *Virology* 2022;**576**:61–8.
3. Wang R, Sun C, Ma J, Yu C, Kong D, Chen M, et al. A bivalent COVID-19 vaccine based on alpha and beta variants elicits potent and broad immune responses in mice against SARS-CoV-2 variants. *Vaccines (Basel)* 2022;**10**:702.
4. Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb ML, Corey L, et al. Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) COVID-19 vaccine. *N Engl J Med* 2021;**385**:2348–60.
5. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021;**384**:403–16.
6. GeurtsvanKessel CH, Geers D, Schmitz KS, Mykytyn AZ, Lamers MM, Bogers S, et al. Divergent SARS-CoV-2 Omicron-reactive T and B cell responses in COVID-19 vaccine recipients. *Sci Immunol* 2022;**7**:eabo2202.
7. Angkasekwinai N, Sewatanon J, Niyomnaitham S, Phumiamorn S, Sukapirom K, Sapsutthipas S, et al. Comparison of safety and immunogenicity of CoronaVac and ChAdOx1 against the SARS-CoV-2 circulating variants of concern (Alpha, Delta, Beta) in Thai healthcare workers. *Vaccine X* 2022;**10**:100153.
8. Schubert M, Bertoglio F, Steinke S, Heine PA, Ynga-Durand MA, Maass H, et al. Human serum from SARS-CoV-2-vaccinated and COVID-19 patients shows reduced binding to the RBD of SARS-CoV-2 Omicron variant. *BMC Med* 2022;**20**:102.
9. Cheng S, Mok C, Leung Y, Ng SS, Chan K, Ko FW, et al. Neutralizing antibodies against the SARS-CoV-2 Omicron variant BA.1 following homologous and heterologous CoronaVac or BNT162b2 vaccination. *Nat Med* 2022;**28**:486–9.
10. Edara VV, Manning KE, Ellis M, Lai L, Moore KM, Foster SL, et al. mRNA-1273 and BNT162b2 mRNA vaccines have reduced neutralizing activity against the SARS-CoV-2 omicron variant. *Cell Rep Med* 2022;**3**:100529.

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