Safety, immunogenicity, and efficacy of a modified COVID-19 mRNA vaccine, SW-BIC-213, in healthy people aged 18 years and above: a phase 3 double-blinded, randomized, parallel controlled clinical trial in Lao PDR (Laos)

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Summary

Background The mRNA vaccine has demonstrated significant effectiveness in protecting against SARS-CoV-2 during the pandemic, including against severe forms of the disease caused by emerging variants. In this study, we examined safety, immunogenicity, and relative efficacy of a heterologous booster of the lipopolyplex (LPP)-based mRNA vaccine (SW-BIC-213) versus a homologous booster of an inactivated vaccine (BBIBP) in Laos.

Methods In this phase 3 clinical trial, which was randomized, parallel controlled and double-blinded, healthy adults aged 18 years and above were recruited from the Southern Savannakhet Provincial Hospital and Champhone District Hospital. The primary outcomes were safety and immunogenicity, with efficacy as an exploratory endpoint. Participants who were fully immunized with a two-dose inactivated vaccine for more than 6 months were assigned equally to either the SW-BIC-213 group (25 μg) or BBIBP group. The primary safety endpoint was to describe the safety profile of all participants in each group up to 6 months post-booster immunization. The primary immunogenic outcome was to demonstrate the superiority of the neutralizing antibody response, in terms of geometric mean titers (GMTs) of SW-BIC-213, compared with BBIBP 28 days after the booster dose. The exploratory efficacy endpoint aimed to assess the relative efficacy of SW-BIC-213 compared to BBIBP against virologically confirmed symptomatic COVID-19 over a 6-month period. The trial was registered with ClinicalTrials.gov (NCT05580159).

Findings Between October 10, 2022, and January 13, 2023, 1200 participants were assigned to SW-BIC-213 group and 1203 participants in the BBIBP group. All adverse reactions observed during the study were tolerable, transient, and resolved spontaneously. Solicited local reactions were the main adverse reactions in both the SW-BIC-213 group (43.8%) and BBIBP group (14.8%) ($p < 0.001$). Heterologous boosting with SW-BIC-213 induced higher live virus neutralizing antibodies to SARS-CoV-2 wildtype and BA.5 strains with GMTs reaching 750.1 and 192.9 than homologous boosting with BBIBP with GMTs of 131.5 ($p < 0.001$) and 47.5 ($p < 0.001$) on day 29. The statistical findings revealed that, following a period of 14-day to 6-month after booster vaccination, the SW-BIC-213 group exhibited a relative vaccine efficacy (VE) of 70.1% (95% CI: 34.2–86.4) against symptomatic COVID-19 when compared to the BBIBP group.

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Interpretation A heterologous booster with the COVID-19 mRNA vaccine SW-BIC-213 manifests a favorable safety profile and proves highly immunogenic and efficacious in preventing symptomatic COVID-19 in individuals who have previously received two doses of inactivated vaccine.

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Keywords: SARS-CoV-2; COVID-19; mRNA vaccine; Lipopolyplex (LPP); Heterologous boosting; Phase 3 trial

Research in context

Evidence before this study

We searched the PubMed for published research articles in English from database inception to October 20, 2023, using the terms of '(SARS-CoV-2) AND (COVID-19) AND (mRNA vaccine) AND (clinical trial) AND (heterologous booster).' We identified four published clinical trials that explored the effects of heterologous boosting with mRNA vaccines, specifically mRNA-1273 (Moderna, USA), BNT162b2 (Pfizer-BioNTech, Germany), CS-2034 (CanSinoBio, PRC), and SW-BIC-213 (the same vaccine used in this study, approved in Laos, Stemirna, PRC). These trials involved individuals who had received two priming doses of an inactivated vaccine. Notably, all vaccines demonstrated a significant increase in neutralizing antibody titers against multiple variants following the third heterologous booster. Additionally, as reported in phase 1/2 trials in Laos, the safety profile of lipopolyplex (LPP)-based mRNA vaccine SW-BIC-213 was comparable to that of the approved lipid nanoparticle (LNP)-based mRNA vaccine.

Added value of this study

In this first double-blinded phase 3 clinical trial, we provided a comprehensive evaluation of the safety, immunogenicity, and efficacy of the mRNA vaccine SW-BIC-213 as a heterologous booster in healthy individuals who received two doses of the inactivated vaccine (BBIBP) at least 6 months ago. This trial demonstrated that heterologous boosting with SW-BIC-213 had an acceptable safety profile and higher neutralizing antibody titers against both wild-type SARS-CoV-2 and the Omicron variants BA.5 and XBB, compared to homologous boosting with BBIBP. Our results reveal that the relative vaccine efficacy of SW-BIC-213 compared to BBIBP was 70.1% (95% CI: 34.2–86.4) in preventing symptomatic COVID-19.

Implications of all the available evidence

These findings demonstrated that administering a heterologous boost with the mRNA vaccine SW-BIC-213 after a 2-dose primary inactivated vaccine regimen in healthy individuals elicits more robust immune responses compared to homologous boosting, providing protection against symptomatic COVID-19.

Introduction

SARS-CoV-2 primarily spreads through respiratory droplets and close contact. As of 18 October 2023, there were 771.41 million confirmed cases of COVID-19 worldwide, including 6.97 million deaths, reported to WHO (World Health Organization).[1] Development of vaccines using various technologies holds great promise in containing spread of the virus worldwide. At present, a variety of COVID-19 vaccines have been marketed around the world, including inactivated vaccines (SINOVAC Biotechnology, Sinopharm Group/Beijing Bio-Institute of Biological Products, Sinopharm Group/Wuhan Institute of Biological Products), viral vector vaccines (CanSinoBIO, AstraZeneca/Oxford, Janssen), mRNA vaccines (BioNTech/Pfizer, Moderna). Although these vaccines were shown to provide excellent protection against severe COVID-19, waning immunity was observed 6 months after completing two doses of immunization,[2,3] which partially contributed to the reduced vaccine effectiveness against infection and disease.[4,5]

Novel variants of SARS-CoV-2 can escape from established immune barrier provided by vaccine, highlighting the need for effective booster vaccination strategies.[6–9] Heterologous booster is regarded as a promising approach, as exemplified by the study that inactivated vaccine priming followed by mRNA vaccine or adenovirus vaccine boosting augmented immune response compared to the homologous boosting.[10–14] A previous study demonstrated that administering an adenovirus-based vaccine (Ad5-nCoV) as a third dose to individuals who had already received two doses of inactivated vaccine (CoronaVac) resulted in significantly increased immune responses compared to homologous boosting with CoronaVac.[14] Another study revealed that heterologous booster vaccination with BNT162b2,

Ad26.COV2-S, or ChAdOx1 augmented humoral immune responses more than homologous booster vaccination in recipients who had previously received two doses of CoronaVac.[13] In addition, heterologous vaccination can overcome issues related to waning immunity and offer protection against new variants by inducing a broader spectrum of neutralizing antibodies.[15] Moreover, combination of different vaccine platforms provides more flexibility in vaccine administration and logistics, which may be particularly important in settings with limited vaccine supply or in populations with pre-existing immune conditions.

A phase 1/2 clinical trial of SW-BIC-213, a lipopolyplex (LPP)-based mRNA vaccine, has been conducted in Laos, revealing an anticipated favorable safety and immunogenicity profile.[16] Notably, the dosage of 25 μg exhibited superior safety performance, no substantial distinctions emerged between the 25 μg and 45 μg groups in terms of neutralizing antibodies or S-protein specific binding antibodies.[16] Based on these findings, considering that inactivated COVID-19 vaccines have been widely administered as primary series, 25 μg was selected as the booster dosage for the phase 3 study.

Here, we present the results of a phase 3 clinical trial conducted in Laos to evaluate safety, immunogenicity, and efficacy of SW-BIC-213 involving administration of a heterologous booster using the mRNA vaccine in healthy participants who have previously received two doses of an inactivated vaccine.

Methods

Study design and participants

This was a randomized, double-blinded, parallel controlled trial aimed at evaluating safety, immunogenicity, and efficacy of SW-BIC-213, an mRNA booster vaccine. Participants were recruited from Savannakhet Provincial Hospital and Champhone District Hospital, two healthcare facilities in Southern Savannakhet province, Laos. Participants underwent a thorough physical examination, including assessment of vital signs, PCR testing for SARS-CoV-2, and urine pregnancy testing. In addition, the investigators verified vaccination record of each participant. A detailed list of the inclusion and exclusion criteria is provided in the Appendix 1. Healthy participants aged 18 and above, who had received two doses of COVID-19 inactivated vaccine (BBIBP) as the primary regimen, were randomly assigned in a 1:1 ratio to receive a booster shot of either BBIBP or 25 μg SW-BIC-213. Study visits were conducted on days 1, 8, 15, 29, 91, and 181 post-booster immunization. This report includes analysis of immunogenicity data up to 91 days post-vaccination, as well as safety and efficacy data up to day 181 post-booster immunization.

Outcomes

The primary outcomes of this trial included the occurrence of adverse events within 30 min after injection, solicited local reactions and solicited systemic reactions up to 7 days post-booster immunization, unsolicited events up to 28 days after the booster dose, serious adverse events and adverse events of special interest throughout the 6-month study duration, as well as demonstrating the superiority of investigational vaccine in neutralizing antibody on day 29.

As for the secondary outcomes, neutralizing/binding antibodies were measured on days 1, 8, 15, 29 and 91. The first 100 participants were included for detecting geometric mean titers (GMTs) of neutralizing antibodies against SARS-CoV-2 wildtype and BA.5 live virus on days 1, 15, and 29, and XBB.1.9.1 live virus on days 1 and 15. The first 400 participants were included for evaluation of GMTs of neutralizing antibodies against SARS-CoV-2 wildtype and BA.5 pseudovirus as well as GMTs of S protein-specific binding antibodies on days 1, 8, 15, 29, and 91. The study also analyzed the GMT fold increase (GMI) and seroconversion rate of neutralization/binding antibodies post-vaccination relative to day 1 on days 8, 15, 29, and 91. The initial plan was to track immunogenicity up to 181 days post-booster immunization. However, based on our knowledge about other COVID-19 vaccines against the Omicron strains and our understanding of the SW-BIC-213 vaccine, we decided to track immunogenicity up to 91 days instead of 181 days in the study.

The exploratory outcomes included the detection of cellular immunity and the assessment of vaccine efficacy. As for the cellular immunity, 60 randomly selected participants (the final analysis included 56 participants after four withdrew) were included for the examination of SARS-CoV-2 spike protein-specific INF-γ, IL-2, and IL-4 ELISpot responses on days 1, 8, and 15 post-booster administration. The vaccine efficacy endpoint was the incidence of virologically confirmed COVID-19 like illness as defined by specified clinical symptoms and signs and confirmed by a positive result for SARS-CoV-2 nucleic acid viral detection assay, occurring from 14 days to 6 months post-booster immunization.

Randomization and blinding

The randomization was stratified by the age group (18–55 years and ≥56 years). The statistician responsible for randomization utilized the RTSM (Randomization and Trial Supply Management) system to produce two lists: a participant random code list and an investigational product number list. Once a participant's eligibility was confirmed, they were assigned a random code by the investigator, and the study staff then used the Interactive Web Response System (IWRS) to automatically match the investigational product number to the participant random code. On-site, there were non-blinded CRAs and non-blinded investigators. The non-blinded investigators included vaccine administrators and non-blinded nurses. The non-blinded CRAs trained the relevant investigators on maintaining the blind state.

Except for the unblinded team, both investigators and participants were unaware of the participant's group allocation during the trial.

Ethics statement

Before initiation of the study, the trial was approved by the Independent Ethics Committee of the Lao People's Democratic Republic Ministry of Health, specifically the National Ethics Committee for Health Research. Each participant signed informed consent form before involving any process of the study. Throughout the entire duration of this study, the ethics committee provided continuous oversight to identify any ethical concerns that could potentially harm the participants. The study was conducted in compliance with the ethical principles that had their origin in the Declaration of Helsinki, Good Clinical Practice (GCP) and applicable regulatory requirements.

Safety assessment

We monitored adverse events to the investigational product using both solicited and unsolicited methods. Adverse event monitoring was obtained by inquiring about the subject's recent status during each visit and referring to the information recorded by the subjects on the diary/contact cards. Safety assessment included the occurrence of adverse events within 30 min after injection. The safety assessment also included solicited local reactions (pain, swelling, redness) and solicited systemic reactions (fever, headache, muscle pain, fatigue, joint pain, chills and vomiting) up to 7 days post-booster vaccination. Additionally, the study investigated unsolicited events within 28 days post-booster immunization as well as serious adverse events (SAEs) and adverse events of special interest (AESIs) throughout the 6-month study duration.

Efficacy assessment

The relative vaccine efficacy was the exploratory outcomes. COVID-19 cases definitions were established according to the living guidance of NMPA (China's National Medical Products Administration),[17] WHO[18] and FDA (U.S. Food and Drug Administration), and the clinical characteristics of Omicron and practicality on site. COVID-19 cases in the treatment group and the control group were collected from the onset after booster immunization, and relative efficacy was assessed based on the valid COVID-19 cases collected 14 days post-booster immunization (i.e., day 15).

All participants were required to conduct a weekly self-test for antigen using a rapid antigen test kit (ATK). If a participant developed any one or more of the following symptoms: fever, cough, shortness of breath, chills, fatigue, muscle pain, sore throat, nasal congestion, headache, diarrhea, nausea, vomiting, runny nose and loss of reduction of smell/taste, they were instructed to perform an additional self-test for antigen. A positive ATK result required the participant to contact investigators and undergo nasal/throat swab sampling for an RT-PCR test at a designated medical institution. Participants detected as positive in both ATK and RT-PCR were considered confirmatory COVID-19 cases. An independent endpoint assessment committee (EAC) was established to evaluate all confirmatory COVID-19 cases, ultimately determining valid cases and assessing the severity of each case (Fig. S2). Asymptomatic COVID-19 cases were defined as the participant who did not develop any symptoms listed above but both ATK and RT-PCR were positive. Severe COVID-19 cases were defined as valid COVID-19 cases with any one or more symptoms listed above and meeting any one of the following criteria: 1) clinical signs indicative of severe systemic illness, respiratory rate $\geq$30 per minute, heart rate $\geq$125 beats per minute, SpO2 $\leq$93% on room air at sea level or PaO2/FIO2 <300 mm Hg, OR 2) respiratory failure or acute respiratory distress syndrome (ARDS) (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure <90 mmHg, diastolic BP <60 mmHg or requiring vasopressors), OR 3) Significant acute renal, hepatic or neurologic dysfunction, OR 4) Admission to an intensive care unit or death.

Procedures

The SW-BIC-213 vaccine was composed of mRNA that encoded the full-length spike glycoprotein of the prototype Wuhan-HU-1 isolate with artificial mutations (K986P/V987P (pre-fusion structure) mutation, 682-QSAQ-685 mutation (substitution of furin cleavage site) and D614G mutation), which was formulated with lipopolyplex. It was developed and manufactured in accordance with good manufacturing practice guidelines by Stemirna Therapeutics Co., Ltd., Shanghai, China. The vaccine was supplied in a buffered-liquid solution containing 50 μg per 0.5 mL in a vial and stored at –25 °C to –15 °C before use. The BBIBP vaccine used in the study was an inactivated vaccine with aluminum hydroxide as the adjuvant (0.5 ml per dose). It was developed by the Beijing Bio-Institute of Biological Products in China. Participants received a single dose of either the SW-BIC-213 vaccine at a dosage of 25 μg or the inactivated vaccine in their upper arm deltoid. After administration, the subjects were guided to the observation area for a 30-min medical observation and then were required to record of any solicited or unsolicited adverse events within 1–29 days, and other specific adverse events (SAEs, AESIs) until the end of the trial. The data included in this report were the safety data until the end of the study (6 months duration), and immunogenicity data up to day 91 post-booster vaccination. The detailed protocols of antibody titers and ELISpot assay were included in the Appendix 4.

Statistical analysis

In this study, the initial assumption was a standard deviation of 0.6 for the log10-transformed antibody titer.

The anticipated geometric mean titer at day 29 in the treatment group was expected to be 1.4 times higher than that of the control group, aiming for 93% statistical power at a one-sided significance level of 2.5%. This required a minimum of 399 subjects in each group to detect the expected difference. The theory accounted for a discontinuation rate of 20%, the necessary sample size increased to 500 subjects per group. In order to achieve the power for both the 18–55 years and ≥56 years age groups, the sample size for each group were increased to 1000, which resulting in a total sample size of 2000. In the actual enrollment process, due to the limited number of elderly people in Laos, there were no restrictions on the enrollment of individuals aged ≥56 years during the trial's follow-up phase. Eventually, a total of 2268 subjects were enrolled in the 18–55 years age group, while 135 subjects were enrolled in the ≥56 years age group. During the process of clinical trial, new preliminary results from a phase 1 clinical trial revealed promising data on heterologous immunization with the mRNA vaccine SW-BIC-213.[19] Based on the updated information, a recalculation of the sample size for immunogenicity test was conducted. Assuming a standard deviation of 0.6 for the log10-transformed antibody titer, the revised expectation was a geometric mean titer at day 29 in the treatment group 1.6 times higher than that of the control group. Setting the sample size at 200 subjects per group would yield 92.3% statistical power with a one-sided significance level of 2.5% to detect the revised anticipated difference. Consequently, the sample size for immunogenicity test was amended.

The full analysis set (FAS) comprised all randomized participants who complied with the intention-to-treat (ITT) principle, received one booster dose, and had valid pre-vaccination immunogenicity data. The per-protocol set (PPS) comprised randomized participants who met the inclusion criteria, did not meet the exclusion criteria, completed the booster vaccination, and had both valid pre-vaccination immunogenicity data and immunogenicity data after vaccination. The safety set (SS) included all participants who received one booster dose. The PPS was used for immunogenicity analysis and was supplemented by FAS, the SS was used for safety analysis. The number and percentages of participants with adverse events were assessed. Either the $\chi 2$ test or Fisher's exact test was used to analyze categorical data, while the t-test was used to analyze the log-transformed antibody titers. Levels of antibodies against SARS-CoV-2 were reported as GMTs, GMIs (compared to day 1), and seroconversion rates with 95% CI. For demonstrating superiority of investigational vaccine, the log-transformed immunogenicity data on day 29 were included in the Analysis of Covariance (ANCOVA). Treatment and stratification factor (age groups) were fixed effects, and the log-transformed immunogenicity data before booster vaccination were served as the covariate. The adjusted GMT of treatment and control groups was estimated from the ANCOVA model, and the GMT ratio together with 95% confidence interval (CI) between the two groups was derived. If the lower bound of 95% CI was larger than 1, then the superiority result was concluded. Seroconversion was defined as achieving a titer at least four times higher than the pre-dose level for participants with a pre-dose titer ≥ the low limit of quantitation (LLOQ). For participants with initial titers below the LLOQ, seroconversion was defined as equal to or above the LLOQ. Data below the LLOQ were assigned a value of half the threshold. The relative vaccine efficacy was calculated using the formula: 1 – ((incidence rate in the treatment vaccine group)/(incidence rate in the control vaccine group) * 100%). The incidence rate for the treatment group and the control group was calculated by dividing the number of subjects with an event (i.e., the first occurrence of SARS-CoV-2 at least 14 days after the injection) by the number of subjects at risk, adjusted by person-time (years) in each group. The statistical analyses were performed using SAS (version 9.4) or GraphPad Prism 8.0.1. This trial is registered with ClinicalTrials.gov (NCT05580159).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Participants

Between October 10, 2022, and January 13, 2023, a total of 3168 individuals were screened. After excluding 765 ineligible individuals, 2403 eligible participants were randomly assigned to either the COVID-19 inactivated vaccine (BBIBP) or 25 μg mRNA vaccine (SW-BIC-213) booster groups (Fig. 1). The median of the follow-up of all recruited subjects was 183 days (Q1 = 181, Q3 = 185). The mean age of the participants was 35.7 years (SD 12.18; range 18–78). All 2403 participants were healthy adults aged 18 years and above who had completed two doses of inactivated COVID-19 vaccine. Of the participants, 50.3% were male in the SW-BIC-213 group, and 52.6% were male in the BBIBP group. In both groups, over 99% of the participants were Asian, and there were similar body mass index (BMI) values between the SW-BIC-213 and BBIBP groups (Table 1).

Safety

The analysis of adverse events encompassed all 2403 enrolled participants, and the results were summarized in Tables S1–S3. In the SW-BIC-213 group, 331 (27.6%) of 1200 reported grade 1 adverse reactions, 274 (22.8%) of 1200 reported grade 2 adverse reactions, and 1 (0.1%) of 1200 reported grade 3 adverse reaction. In contrast, the BBIBP group had 162 (13.5%) of 1203

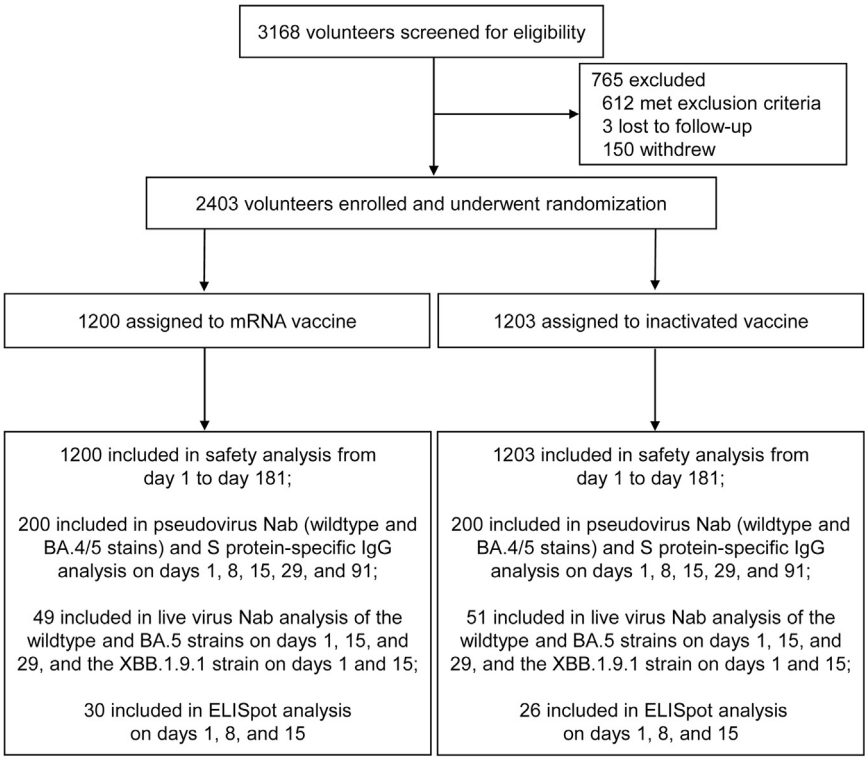

Fig. 1: **Trial profiles.**

	SW-BIC-213 (n = 1200)	BBIBP (n = 1203)	Totality (n = 2403)
Age (years)			
n	1200	1203	2403
Mean (SD)	36.1 (12.18)	35.4 (12.17)	35.7 (12.18)
Median	35.0	34.0	34.0
Q1, Q3	26.5, 45.0	25.0, 44.0	26.0, 45.0
Min, Max	18, 78	18, 75	18, 78
Age group, n (%)			
18–55	1134 (94.5)	1134 (94.3)	2268 (94.4)
≥56	66 (5.5)	69 (5.7)	135 (5.6)
Gender, n (%)			
Male	603 (50.3)	633 (52.6)	1236 (51.4)
Female	597 (49.8)	570 (47.4)	1167 (48.6)
Race, n (%)			
Asian	1200 (100.0)	1202 (99.9)	2402 (100.0)
American Indian or Alaska Native	0 (0.0)	1 (0.1)	1 (0.0)
BMI (kg/m^2)			
n	1200	1203	2403
Mean (SD)	22.67 (3.499)	22.62 (3.504)	22.65 (3.501)
Median	22.00	22.10	22.00
Q1, Q3	20.20, 24.70	20.20, 24.50	20.20, 24.60
Min, Max	14.6, 38.0	13.8, 40.6	13.8, 40.6

Data are no. (%), mean (SD), or median (interquartile, IQR). SD: standard deviation. BMI: body mass index.

Table 1: **Baseline demographic characteristics of participants (full analysis set, FAS).**

reported grade 1 adverse reactions (p < 0.001), 134 (11.1%) of 1203 reported grade 2 adverse reactions (p < 0.001), 1 (0.1%) of 1203 reported grade 3 adverse reaction (p = 1.000) (Table S1).

The most frequently reported solicited reactions in the SW-BIC-213 group were vaccination pain (43.6%) and fever (8.4%), while the BBIBP group reported these less frequently at 14.6% (p < 0.001) and 4.6% (p < 0.001), respectively. Headache was commonly reported reaction in both groups, with no significant difference between the SW-BIC-213 (7.8%) and BBIBP groups (6.8%) (p = 0.348) (Fig. 2, Table 2). As stratified by severity, in both groups, pain at the injection site was limited to grade 1 or 2, mainly grade 1. The incidence of grade 1 and grade 2 pain in the SW-BIC-213 group were 26.0% and 17.6%, respectively. In the BBIBP group, the incidence of grade 1 and grade 2 pain were 9.4% (p < 0.001) and 5.2% (p < 0.001), respectively (Fig. 2, Table S2). The SW-BIC-213 has significantly higher incidence rates of grade 1 and grade 2 pain than the BBIBP group. In regarding of fever and headache, in the SW-BIC-213 group, the incidence of grade 1 and grade 2 fever were 5.1% and 3.3%, respectively, while in the BBIBP group, they were 2.8% (p = 0.005) and 1.7% (p = 0.012), respectively. One case of grade 3 fever was reported in both the SW-BIC-213 and BBIBP groups, accounting for 0.1% each (p = 1.000). In the SW-BIC-213 group, the incidence of grade 1 and grade 2 headache were 4.6% and 3.3%, respectively, while in the BBIBP group, they were 2.9% (p = 0.032) and 3.9% (p = 0.442), respectively (Fig. 2, Table S2). The SW-BIC-213 exhibited significantly higher incidence rates of grade 1 fever and headache compared to the BBIBP group.

There was no difference between the SW-BIC-213 and BBIBP groups in the rates of related unsolicited adverse events reported within 28 days after the booster (p = 0.814) (Table 2, Tables S1 and S3). Until the end of the study, a total of four serious adverse events (0.2%) was reported, including 1 (0.1%) of 1200 occurred in the SW-BIC-213 group, and 3 (0.2%) of 1203 occurred in the BBIBP group (p = 0.625) (Table S1). None of these serious adverse events were related to vaccination. Moreover, there were no reports of adverse events of special interest in both the SW-BIC-213 and BBIBP groups (Table S1).

Antibody responses

The humoral immunogenicity data was based on full analysis set (FAS). For pseudovirus neutralizing antibodies (Nab) on day 29, the GMT ratios (GMRs) for wildtype and BA.4/5 strains were 9.1 (95% CI: 7.8, 10.6) and 9.28 (95% CI: 7.83, 11.00), respectively. For live virus Nab on day 29, the GMRs for wildtype and BA.5 strains were 5.7 (95% CI: 3.6, 8.8) and 4.9 (95% CI: 3.8, 6.4), respectively. In all instances, the lower bound of the 95% CI exceeded 1, meeting the predefined superiority criteria. Therefore, the heterologous booster with SW-BIC-213 was superior to the homologous booster with BBIBP (Fig. 3, Tables S4–S7).

A total of 200 participants were included in the SW-BIC-213 group, while another 200 participants were included in the BBIBP group for pseudovirus Nab analysis (Fig. 3A and B, Tables S4 and S5). Concerning pseudovirus Nab against the wildtype strain, at the baseline (day 1), GMTs were 777.8 and 913.0 in the SW-BIC-213 and BBIBP groups, respectively (p = 0.340) (Fig. 3A). On days 15, 29 and 91 after booster immunization, GMTs increased to 20228.5 and 12616.5 and 4123.7 in the SW-BIC-213 group, and 1794.3 (p < 0.001) and 1446.7 (p < 0.001) and 1061.3 (p < 0.001) in the BBIBP group, respectively (Fig. 3A, Table S4). The SW-BIC-213-induced pseudovirus Nab levels against the wildtype strain were 11.27-, 8.72-, and 3.89-fold higher than those induced by BBIBP on days 15, 29, and 91, respectively. Regarding pseudovirus Nab against the

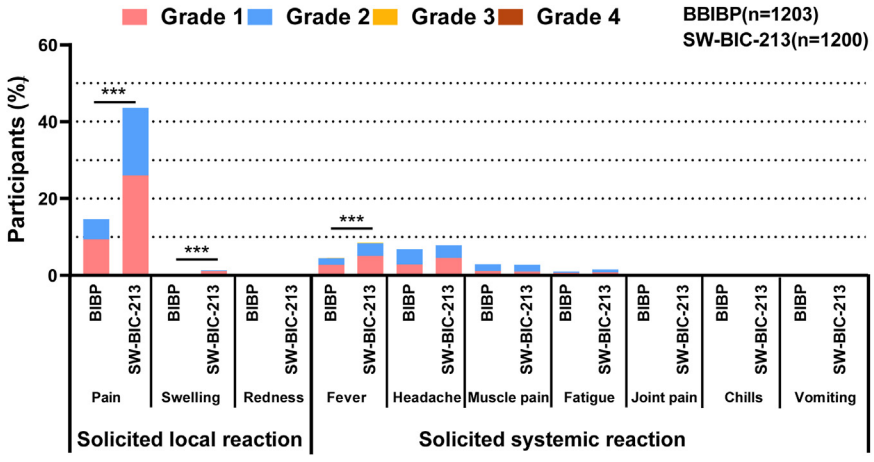

Fig. 2: Safety of heterologous boosting with SW-BIC-213.

Items	SW-BIC-213 (n = 1200)	BBIBP (n = 1203)	Totality (n = 2403)	p value
	n (%)	n (%)	n (%)	
Solicited AE	604 (50.3)	295 (24.5)	899 (37.4)	<0.001
Solicited systemic reaction	199 (16.6)	154 (12.8)	353 (14.7)	0.009
Fever	101 (8.4)	55 (4.6)	156 (6.5)	<0.001
Fatigue	18 (1.5)	12 (1.0)	30 (1.2)	0.278
Headache	94 (7.8)	82 (6.8)	176 (7.3)	0.348
Chills	2 (0.2)	2 (0.2)	4 (0.2)	1.000
Vomiting	2 (0.2)	1 (0.1)	3 (0.1)	0.624
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	–
Muscle pain	33 (2.8)	35 (2.9)	68 (2.8)	0.902
Joint pain	2 (0.2)	3 (0.2)	5 (0.2)	1.000
Solicited local reaction	526 (43.8)	178 (14.8)	704 (29.3)	<0.001
Pain	523 (43.6)	176 (14.6)	699 (29.1)	<0.001
Swelling	15 (1.3)	1 (0.1)	16 (0.7)	<0.001
Redness	5 (0.4)	2 (0.2)	7 (0.3)	0.288
Unsolicited AE	9 (0.8)	8 (0.7)	17 (0.7)	0.814
Eye disorders	4 (0.3)	1 (0.1)	5 (0.2)	0.218
Vision blurred	4 (0.3)	1 (0.1)	5 (0.2)	0.218
Nervous system disorders	4 (0.3)	2 (0.2)	6 (0.2)	0.452
Hypoaesthesia	1 (0.1)	1 (0.1)	2 (0.1)	1.000
Dizziness	2 (0.2)	1 (0.1)	3 (0.1)	0.624
Tremor	1 (0.1)	0 (0.0)	1 (0.0)	0.499
General disorders and administration site conditions	1 (0.1)	2 (0.2)	3 (0.1)	1.000
Chest pain	0 (0.0)	1 (0.1)	1 (0.0)	1.000
Pyrexia	1 (0.1)	1 (0.1)	2 (0.1)	1.000
Infections and infestations	0 (0.0)	2 (0.2)	2 (0.1)	0.500
Nasopharyngitis	0 (0.0)	2 (0.2)	2 (0.1)	0.500
Musculoskeletal and connective tissue disorders	1 (0.1)	1 (0.1)	2 (0.1)	1.000
Muscular weakness	1 (0.1)	0 (0.0)	1 (0.0)	0.499
Pain in extremity	0 (0.0)	1 (0.1)	1 (0.0)	1.000
Ear and labyrinth disorders	1 (0.1)	0 (0.0)	1 (0.04)	0.499
Tinnitus	1 (0.1)	0 (0.0)	1 (0.04)	0.499
Respiratory, thoracic and mediastinal disorders	1 (0.1)	1 (0.1)	2 (0.1)	1.000
Dyspnoea	1 (0.1)	0 (0.0)	1 (0.0)	0.499
Epistaxis	1 (0.1)	0 (0.0)	1 (0.0)	0.499
Oropharyngeal pain	0 (0.0)	1 (0.1)	1 (0.0)	1.000
Skin and subcutaneous tissue disorders	2 (0.2)	0 (0.0)	2 (0.1)	0.249
Pruritus	1 (0.1)	0 (0.0)	1 (0.0)	0.499
Rash	1 (0.1)	0 (0.0)	1 (0.0)	0.499

Data are n (%), n, the number of participants; %, the proportion of participants. The test $\chi 2$ was used to compare between SW-BIC-213 and BBIBP groups. AE: adverse event. TEAE: treat emergent adverse event.

Table 2: **Adverse reaction within 28 days after vaccination (safety set, SS).**

BA.4/5 strain, no difference was observed at the baseline, with GMTs of 53.48 and 64.26 in the SW-BIC-213 and BBIBP groups, respectively (p = 0.315) (Fig. 3B, Table S5). On days 15, 29, and 91 post-booster immunization, GMTs increased to 1323.26, 828.47, and 400.58 in the SW-BIC-213 group, and 127.02 (p < 0.001), 98.40 (p < 0.001), and 105.05 (p < 0.001) in the BBIBP group, respectively (Fig. 3B, Table S5). The SW-BIC-213-induced pseudovirus Nab levels against the BA.4/5 strain were 10.42-, 8.42-, and 3.81-fold higher than those induced by BBIBP on days 15, 29, and 91, respectively. In addition, the GMT fold increases (GMIs) and seroconversion rates of pseudovirus Nab against the wild-type and BA.4/5 strains were higher in the SW-BIC-213 group than that in the BBIBP group on days 8, 15, 29 and 91 (Fig. 3A and B).

Forty-nine participants were included in the SW-BIC-213 group, and fifty-one participants in the BBIBP group for live virus Nab detection (Fig. 3C and D, Fig. S1A, Tables S6–S8). Regarding live virus Nab against the

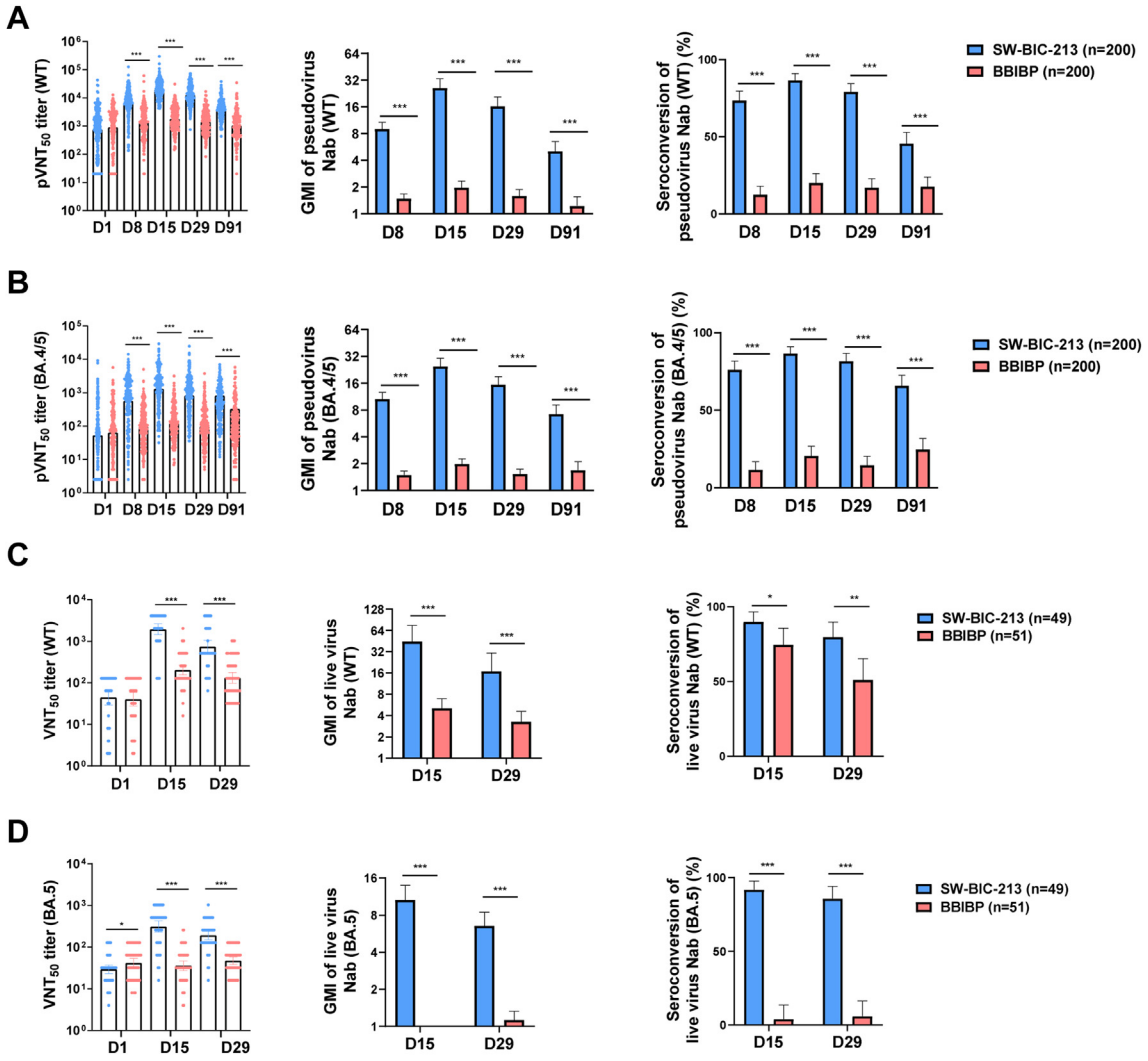

***Fig. 3*: Antibody responses after heterologous boosting with SW-BIC-213 (full analysis set, FAS).** (A) Geometric mean titers (GMTs) (left), GMT fold increases (GMIs) (middle) and seroconversion rates (right) of pseudovirus neutralizing antibody against the wildtype strain of SARS-CoV-2 in SW-BIC-213 group (n = 200 on days 1, 8, 15 and 29; n = 187 on day 91) and BBIBP group (n = 200 on days 1, 8, 15 and 29; n = 182 on day 91). (B) GMTs (left), GMIs (middle) and seroconversion rates (right) of pseudovirus neutralizing antibody against the Omicron BA.4/5 strain of SARS-CoV-2 in SW-BIC-213 group (n = 200 on days 1, 8, 15 and 29; n = 187 on day 91) and BBIBP group (n = 200 on days 1, 8, 15 and 29; n = 182 on day 91). (C) GMTs (left), GMIs (middle) and seroconversion rates (right) of live-virus neutralizing antibody against the wildtype strain of SARS-CoV-2 in SW-BIC-213 group (n = 49) and BBIBP group (n = 51). (D) GMTs (left), GMIs (middle) and seroconversion rates (right) of live-virus neutralizing antibody against the Omicron BA.5 strain of SARS-CoV-2 in SW-BIC-213 group (n = 49) and BBIBP group (n = 51). Data are presented as the GMT (95% CI). n indicated the number of participants. VNT: live virus neutralization titer. pVNT: pseudovirus neutralization titer. Nab: neutralizing antibody. Error bars indicated 95% CIs. *indicates $p < 0.05$, **indicated $p < 0.01$, *** indicates $p < 0.001$.

wildtype strain, at the baseline (day 1), there was no significant difference in GMTs of live virus Nab against the wildtype strain between the SW-BIC-213 and BBIBP groups, with levels reaching 44.3 and 40.3, respectively ($p = 0.736$). However, 14 and 28 days after booster immunization, there was a significant increase in live virus Nab levels, with GMTs reaching 1962.9 and 750.1 in the SW-BIC-213 group, and 203.2 and 131.5 in the BBIBP group, respectively (day 15 $p < 0.001$, day 29 $p < 0.001$) (Fig. 3C, Table S6). The SW-BIC-213-induced live virus Nab levels against the wildtype strain were 9.66- and 5.70-fold higher than those induced by BBIBP on days 15 and 29, respectively. Regarding live virus Nab against the BA.5 strain, GMTs at the baseline were 29.4 and 42.0 in the SW-BIC-213 and BBIBP groups, respectively ($p = 0.036$). The titer increased to 312.1 on day 15 and 192.9 on day 29 in the SW-BIC-213 group. In contrast, in the BBIBP group, GMTs were only 35.7 on day 15

($p < 0.001$) and 47.5 on day 29 ($p < 0.001$) (Fig. 3D, Table S7). The SW-BIC-213-induced live virus Nab levels against the BA.5 strain were 8.74- and 4.06-fold higher than those induced by BBIBP on days 15 and 29, respectively. Moreover, the GMIs and seroconversion rates of live virus Nab against the wildtype and BA.5 strains were higher in the SW-BIC-213 group than that in the BBIBP group on days 15 and 29 (Fig. 3A and B). The study also evaluated the live virus Nab against the XBB.1.9.1 variant and found that on day 15, SW-BIC-213 induced a GMT of 40.4, while BBIBP only resulted in 6.2 (Fig. S1A, Table S8). The SW-BIC-213-induced live virus Nab levels against the XBB.1.9.1 strain were 6.52-fold higher than those induced by BBIBP on day 15.

Two hundred participants were included in both the SW-BIC-213 and BBIBP groups for S protein-specific binding antibody detection. The results showed that the SW-BIC-213 booster elicited stronger binding antibody levels than the booster by BBIBP. Specifically, by day 15, the GMTs reached 3898.6 IU/mL for the SW-BIC-213 group and 315.5 IU/mL for the BBIBP group ($p < 0.001$). By day 29, the GMTs were 2544.7 IU/mL for the SW-BIC-213 group and 260.2 IU/mL for the BBIBP group ($p < 0.001$). By day 91, the GMTs were 950.1 IU/mL for the SW-BIC-213 group and 277.8 IU/mL for the BBIBP group ($p < 0.001$) (Fig. S1B, Table S9). Taken together, these results indicated that heterologous booster with SW-BIC-213 was a more effective strategy to enhance antibody responses in inactivated vaccine-immunized individuals compared to homologous booster of BBIBP vaccine.

T-cell responses

The cellular immunity data was based on full analysis set. For exploratory outcomes related to T-cell responses, a total of 60 subjects were initially randomly selected. However, 4 participants withdrew from the study, resulting in 56 participants being included in the analysis. Among these, 30 subjects received the SW-BIC-213 booster, while 26 subjects received the BBIBP booster. The functionality of T cells induced by the vaccine were evaluated by measuring the secretion of IFN-γ, IL-2, and IL-4 cytokines using the ELISpot method with fresh whole blood samples. At baseline, the mean IFN-γ, IL-2, and IL-4 spots were comparable between the SW-BIC-213 and BBIBP groups. However, after the booster vaccination, the mean spots for all three cytokines were significantly higher in the SW-BIC-213 group than in the BBIBP group on days 8 and 15 (Fig. 4A–C). Specifically, at day 8, the mean IFN-γ spots increased to 128 and 16 ($p < 0.001$), the mean IL-2 spots increased to 82 and 15 ($p < 0.001$), and the mean IL-4 spots increased to 48 and 2 ($p < 0.001$) in the SW-BIC-213 and BBIBP groups, respectively (Fig. 4A–C). These findings indicated that a heterologous mRNA vaccine booster effectively activated cellular immunity in individuals who were primarily immunized with two doses of inactivated vaccine.

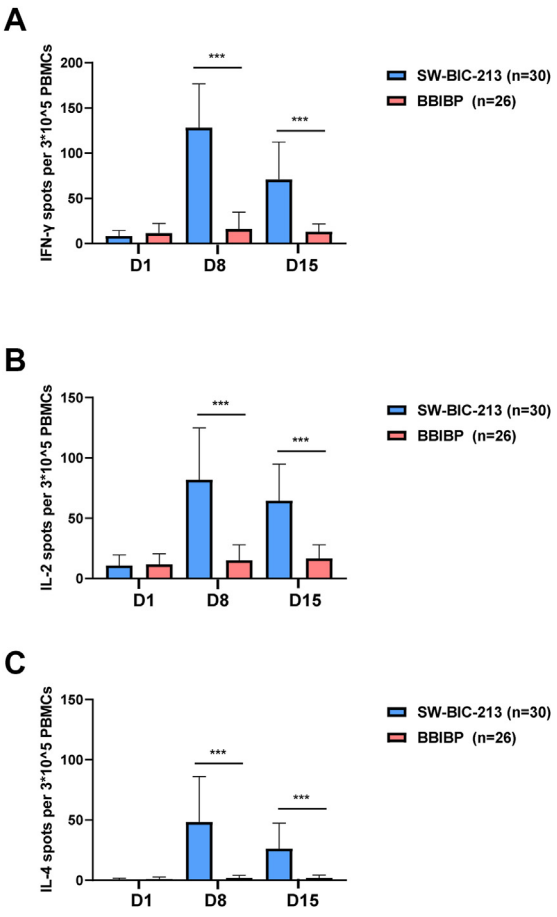

Fig. 4: **T-cell responses after heterologous boosting with SW-BIC-213 (full analysis set, FAS).** (A) IFN-γ-secreting T cells were analyzed by ELISpot assay on days 1, 8 and 15 post-booster immunization in SW-BIC-213 group (n = 30) and BBIBP group (n = 26). (B) IL-2-secreting T cells were analyzed by ELISpot assay on days 1, 8 and 15 post-booster immunization in SW-BIC-213 group (n = 30) and BBIBP group (n = 26). (C) IL-4-secreting T cells were analyzed by ELISpot assay on days 1, 8 and 15 post-booster immunization in SW-BIC-213 group (n = 30) and BBIBP group (n = 26). Data are presented as the mean (SD) of spot counts per 3*10^5 PBMC. n indicated the number of participants. ELISpot: enzyme-linked immunospot. PBMC: peripheral blood mononuclear cells. *** indicates $p < 0.001$.

Efficacy

For exploratory outcomes with efficacy, after evaluation by the endpoints assessment committee (EAC), valid cases were ultimately confirmed and the severity of each case was assessed (Fig. S2). A total of 40 valid COVID-19 cases were identified within 6 months post-booster immunization, and no severe cases were observed. These cases consisted of 39 mild cases and 1 asymptomatic case. Five cases (including one asymptomatic infection case) occurred within 14 days after booster vaccination. Among the cases that occurred from 14 days to 6 months post-booster

Time range	SARS-CoV-2 infection cases		Person-years[a]		Incidence rate (95%CI)[b]		Relative vaccine efficacy (95% CI)
	SW-BIC-213 (n = 1200)	BBIBP (n = 1203)	SW-BIC-213 (n = 1200)	BBIBP (n = 1203)	SW-BIC-213 (n = 1200)	BBIBP (n = 1203)	
Day 14–Month 3	4.0	9.0	523.9	528.9	7.6 (2.9, 20.3)	17.0 (8.9, 32.7)	55.1 (−45.7, 86.2)
Month 3–Month6	4.0	18.0	523.9	528.9	7.6 (2.9, 20.3)	34.0 (21.4, 54.0)	77.6 (33.7, 92.4)
Day 14–Month 6	8.0	27.0	523.9	528.9	15.3 (7.6, 30.5)	51.0 (35.0, 74.4)	70.1 (34.2, 86.4)

[a]Person-years were defined as the total years from randomization date to the earliest among the date of symptomatic SARS-CoV-2 infection, last date of study participation, and data cutoff date. [b]The incidence rate was defined as the number of participants with an event divided by the number at risk, adjusted by person-years (total time at risk) in each treatment group. The 95% confidence interval was calculated using the exact method (Poisson distribution), conditional on the total number of events adjusted by person-years.

Table 3: **Vaccine efficacy within 14 days–6 months (randomization set, RDS).**

vaccination, a total of 35 valid infection cases were reported. Within the SW-BIC-213 group, 8 cases occurred and all exhibiting mild symptoms, with an incidence rate of 15.3 per 1000 people per year (95% CI: 7.6, 30.5). 27 cases were observed in the BBIBP group, all characterized as mild, with an incidence rate of 51.0 per 1000 people per year (95% CI: 35.0, 74.4). By comparing the SW-BIC-213 to the BBIBP vaccine, the relative vaccine efficacy (rVE) was determined to be 70.1% (95% CI: 34.2%, 86.4%) against symptomatic COVID-19 within the period of 14-day to 6-month post-booster immunization (Table 3). Due to the failure of sample collection or extraction, the virus variants causing infection were sequenced for only 20 cases, most of which were Omicron XBB-related variants (Table S10).

Discussion

In this study of phase 3 trial, we evaluate the safety, immunogenicity, and efficacy of a core–shell structured LPP-based mRNA vaccine SW-BIC-213 as a heterologous COVID-19 mRNA booster in healthy people aged 18 years and above in Laos.

The adverse reactions observed during the study process were generally tolerable, mostly transient, and resolved spontaneously. The severity of these adverse reactions was mainly limited to grade 1–2, with only one case of vaccination-related grade 3 fever reported in the SW-BIC-213 and BBIBP vaccine groups, respectively. There were no reports of vaccine-related SAEs and AEISs as of the end of the study. Both the SW-BIC-213 and BBIBP groups exhibited local solicited reactions, particularly vaccination site pain. Although the incidence of adverse reactions was relatively higher in the SW-BIC-213 group than the BBIBP group, these incidences and severities were acceptable and showed good tolerance. Overall, SW-BIC-213 demonstrated a favorable safety profile, with predominantly mild to moderate reactogenicity compared to other similar mRNA vaccine products.

Heterologous vaccine boosting strategies have been wildly used to enhance immunization against SARS-CoV-2, especially in individuals who received inactivated or adenovirus vaccines as their primary dose, followed by a booster with mRNA vaccines, which promoted immune responses.[20–22] As an investigational COVID-19 mRNA vaccine, SW-BIC-213 distinguishes itself from approved COVID-19 vaccines by utilizing the LPP delivery system. This delivery system comprises a core–shell structure that provides a proper mRNA virus-like structure, thereby facilitating recognition by the phagocytic antigen-presenting cells. Consequently, this recognition significantly enhances vaccine uptake and elicits robust humoral and cellular immune responses, as evidenced by a preclinical study,[23] an investigator-initiated trial,[24] a phase 1 trial in China[19] and a phase1/2 trial in Laos.[16] Our study revealed that, as a heterologous booster regimen with mRNA vaccine, SW-BIC-213 induced stronger neutralizing antibody responses against live virus of the wildtype, BA.5 and XBB.1.9.1 strains of SARS-CoV-2, as well as pseudovirus-mediated neutralizing antibodies of the wildtype and BA.4/5, compared to the homologous booster using BBIBP. Nonetheless, SW-BIC-213 vaccination resulted in a higher GMI and seroconversion rate as compared to the BBIBP. These findings suggest that heterologous boosting with SW-BIC-213 produced cross-reactive neutralizing antibodies against emerging variants.

T cells have been shown to provide long-lasting immunity against viral infections.[25] While antibodies can wane over time, T cells can persist for years or even decades after vaccination.[26] SW-BIC-213 elicited the stronger cytokine level of IFN-γ, IL-2, and IL-4 as compared to BBIBP after boosting, which is in line with the studies that using a different type of vaccine for the booster shot can enhance T cell responses compared to using the same vaccine, leading to better protection against the target virus or pathogen.[27,28] Furthermore, it was found that SW-BIC-213 induced a higher number of IFN-γ and IL-2-producing T cells than the IL-4-secreting T cells, which demonstrated a dominant Th1-polarized phenotype. Notably, inactivated vaccines are more prone to elicit a Th2-type immune response. By using an mRNA vaccine as a booster, there is a possibility to skew the phenotype towards Th1-biased immune response, which is more favorable for protection against SARS-CoV-2.[29]

There is some evidence regarding the association between immune markers and protection. Feng et al. found that the binding antibody and neutralizing antibody levels are correlated with protection from symptomatic infection, higher antibody levels are associated with greater vaccine efficacy.[30] Khoury et al. illustrated that a high level of neutralizing antibodies is a strong predictor of immune protection against symptomatic SARS-CoV-2 infection.[31] In addition, T cell response may play a crucial role in offering protection.[32–34] Our study demonstrated that, within the 14-day to 6-month period post-booster immunization, SW-BIC-213 exhibited a relative vaccine efficacy of 70.1% against symptomatic COVID-19, in comparison to that of BBIBP. This may be attributed to stronger neutralizing/binding antibody responses and Th1-biased T cell immunity induced by SW-BIC-213.

This study has several limitations. Firstly, due to the restricted number of elderly people in Laos, the study recruited just 135 elderly subjects, a smaller number than the originally intended 1000 elderly subjects. Since the sample size of individuals aged 56 or older was too limited to allow a sub-analysis of the elderly population, we did the analysis of safety, immunogenicity, and efficacy based on the total cohort of participants. As a result, the findings in this study may be primarily limited to the young age population. Secondly, the study did not include a comparison of the mRNA vaccine booster regimen with other heterologous booster regimens such as booster with adenovirus vaccines or protein subunit vaccines. Thirdly, immunogenicity was the primary endpoint, while efficacy was only as an exploratory endpoint in this study, therefore the sample size was restricted. Throughout the 6-month study period, a limited number of infection cases were collected, we could only obtain relative vaccine efficacy data with statistically significant differences. Additionally, the absolute efficacy of this product needs to be evaluated in large-sample protective efficacy studies.

To sum up, the heterologous booster with the LPP-based mRNA vaccine SW-BIC-213 was safe, immunogenic, and effective. To address the pressing need to curb the global COVID-19 pandemic, SW-BIC-213 as a heterologous boosting regimen is a useful option for individuals who have received two doses of an inactivated vaccine.

Contributors

M Mayxay is the principal investigator of this trial. D D, C P, B Yu, Y-Z Wang and R Yan participated in designing the trial and study protocol. X-L Guo, Y-Z Gui and R-J Pei contributed to laboratory testing. M-Y Shen and X-H Qiu contributed to develop and manufacture SW-BIC-213. Y Fang and F-F Zhao contributed to the manuscript writing. Y Li and B Luo participated in the site work, including the recruitment, participants' visits and data collection. S-J Liu contributed to statistical analysis. J-X Li, H Shen, W-X Guan and H-W Li contributed to the critical review and revising of the manuscript. Y Fang, B Yu and C-C Xu contributed to verify the data. Y Fang, S-J Liu and B Yu had access to all the data in the study. All authors reviewed and approved the final version of the manuscript.

Data sharing statement

The study protocol is available for review. The individual participant data will be accessible upon requests directed to the corresponding author.

Declaration of interests

Y Fang, Y Li, M-Y Shen, B Yu, B Luo, Y-Z Wang, S-J Liu, F-F Zhao, C-C Xu, X-H Qiu, R Yan, J Wang, H Shen and H-W Li are employees of Stemirna Therapeutics Co., Ltd. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102372.

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