

A SARS-CoV-2 recombinant spike protein vaccine (S-268019-b) for COVID-19 prevention during the Omicron-dominant period: A phase 3, randomised, placebo-controlled clinical trial

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ABSTRACT

Clinical trials of new vaccines based on existing variants of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) are often impacted by the emergence of new virus variants. We evaluated the efficacy, immunogenicity, and safety of S-268019-b, a recombinant spike protein subunit vaccine based on the ancestral strain, for preventing symptomatic coronavirus disease 2019 (COVID-19) during the Omicron (BA.2)-dominant period in Vietnam. In this multicentre, phase 3, randomised (2:1), observer-blind, placebo-controlled crossover study, participants received 2 intramuscular doses (28 days apart) of either 10 µg of S-268019-b (Recombinant S-protein vaccine) or placebo. The primary endpoint was incidence of laboratory-confirmed symptomatic COVID-19 before crossover, with onset within 14 days following the second dose, in participants who were seronegative and reverse transcription polymerase chain reaction (RT-PCR)-negative at baseline. The secondary endpoints included immunogenicity and safety. In total, 8,594 participants were randomised (S-268019-b [n = 5,727]; placebo [n = 2,867]). Vaccine efficacy versus placebo was 39.1 % (95 % confidence interval [CI]: 26.6–49.5; one-sided P = 0.0723). The incidence rate (95 % CI) of symptomatic COVID-19 was 776.41/1,000 person-years (682.04–880.19) in the S-268019-b group and 1272.87/1,000 person-years (1101.32–1463.57) in the placebo group. The geometric mean titres (95 % CI) of the SARS-CoV-2 neutralising antibody increased on Day 57 versus baseline with S-268019-b (34.66 [27.04–44.41] versus 2.50 (non-estimable) but not with placebo. There were no safety concerns regarding S-268019-b. S-268019-b did not demonstrate the targeted efficacy threshold against symptomatic COVID-19; however, findings were comparable with other prophylactic vaccines based on ancestor strain during the Omicron-dominant period. S-268019-b demonstrated immunogenicity and was well-tolerated.

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1. Introduction

The rapid outbreak and the emergence of highly virulent and transmissible newer variants of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) have caused further mortality, especially in frail populations with comorbidities, and disruption of global health and economy [1]. As per the World Health Organisation (WHO) dashboard

dated 26 July 2023, there have been 768,560,727 confirmed cases of coronavirus disease 2019 (COVID-19), including 6,952,522 deaths globally, and 61,196,155 confirmed cases with 806,561 deaths in South-East Asia alone [2]. In Vietnam, 11,621,626 confirmed cases and 43,206 deaths have been reported to date [3].

Vaccines are crucial in containing the COVID-19 pandemic and averting hospitalisations and deaths globally [4,5]. When developing

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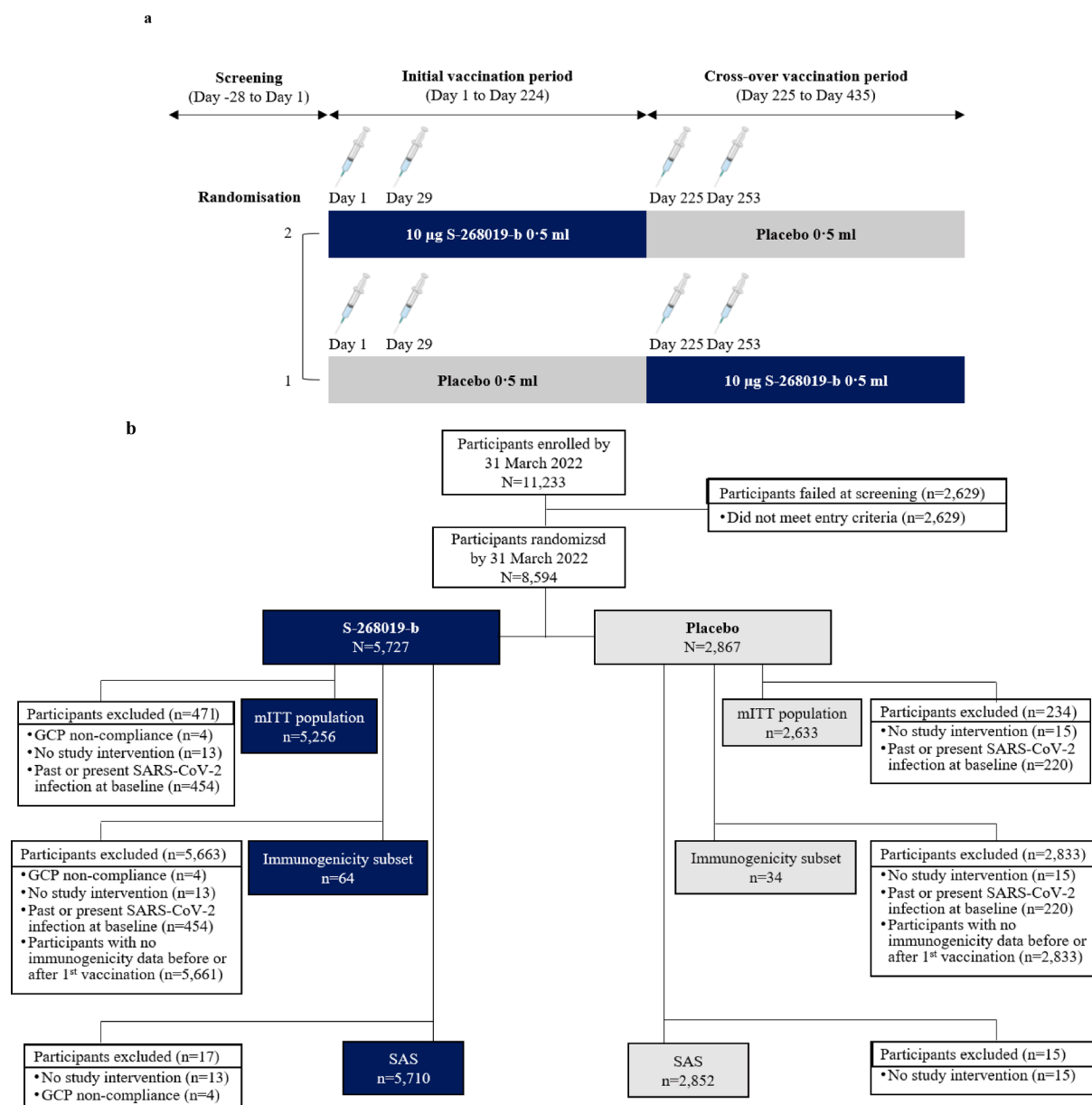


Fig. 1. (a) Study design, and (b) study participant disposition. The SAS populations included all randomised participants receiving at least one dose of the intervention. The mITT population included all randomised participants who received at least one dose of the intervention and were seronegative (RT-PCR negative) for SARS-CoV-2 at baseline. The immunogenicity subset included all randomised participants in the mITT population with a valid immunogenicity test result before and at least one valid result after the first vaccination. mITT, modified intention-to-treat population; n, number of participants in each category; N, total number of participants; S-268019-b, recombinant protein modified from S-protein of SARS-CoV-2 (S-910823) mixed in 1:1 ratio with a squalene-in-water emulsion (A-910823); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAS, safety analysis set.

this publication, over 183 vaccines of various types were in clinical development and 199 in pre-clinical development [6]. Currently, 13 COVID-19 vaccines have been granted Emergency Use Listing by the WHO, including inactivated virus vaccines [7,8]. In Vietnam, 8 COVID-19 vaccines have been approved to date, including three inactivated virus vaccines, two mRNA vaccines, one protein subunit vaccine, and two viral vector vaccines with more than 266 million doses administered thus far [3,9].

Globally, the emergence of highly virulent and transmissible newer variants of concern (VOC) poses novel challenges and limitations to existing therapeutic options, including in Vietnam [4,10,11]. Concerns regarding the reduced effectiveness of neutralising antibodies and immunity elicited against such VOCs by currently available vaccines necessitate the development of novel vaccines which offer effectiveness and safety against SARS-CoV-2 and its variants [4,10]. Currently, the

five VOCs identified by WHO include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) [12,13]. Since mid-February 2022, Vietnam witnessed an Omicron (BA.2)-dominant period, with nearly 80 % of COVID-19 cases due to this Omicron subvariant [14]. These findings necessitated effective preventative and control measures to arrest the transmission, morbidity, and mortality associated with the Omicron subvariant in Vietnam [11]. The details of COVID-19 outbreak, vaccination status and cases in Vietnam are provided in [Supplementary Figs. S1–S4](#).

Through our extensive vaccine research program, we are developing S-268019-b vaccine, a recombinant protein subunit vaccine, to prevent COVID-19 [5–18]. S-268019-b consists of a recombinant spike protein, which is produced in insect cells using the baculovirus expression vector system, and a squalene-based adjuvant [5–18]. Previously, we evaluated S-268019-b in healthy volunteers either as a priming vaccine or as a

booster dose, and demonstrated that it was well-tolerated, and elicited immunogenicity similar to the levels of approved mRNA vaccines [16–18]. However, a prospective study evaluating the vaccine efficacy of S-268019-b was considered necessary. Here, we report the results of a phase 3 study of S-268019-b vaccine assessing the safety and efficacy for preventing symptomatic COVID-19 amongst the adult Vietnamese population, which was conducted during the Omicron (BA.2)-dominant period.

2. Methods

2.1. Study design

This was a phase 3, randomised (2:1), placebo-controlled, observer-blind, crossover study conducted at 22 centres across 15 provinces (with 17 centres across 12 provinces during the initial vaccination period) in Vietnam. Since ethical viewpoints are against including a placebo in a long-term blinded study, a blinded crossover design was adopted. The study consisted of the screening (Day –28 to Day 1), initial vaccination (Day 1 to Day 224), and crossover vaccination periods (Day 225 to Day 435). Following screening for eligible participants, on Day 1 of the initial vaccination period, participants were randomised to receive 2 doses of either S-268019-b or a placebo, and the crossover vaccination period commenced 6 months after the second dose. Those who received S-268019-b in the initial vaccination period proceeded to the crossover vaccination period to receive a placebo and vice-versa (Fig. 1a). The follow-up period is ongoing to assess vaccine efficacy and safety during the crossover vaccination period. The details of SARS-CoV2 cases screened, included, and analysed are provided in [Supplementary Fig. S5](#).

2.2. Study participants

Participants aged ≥ 18 years who could complete the e-diary/paper diary (with the assistance of another family member/community health worker, if required) and who agreed not to participate in another SARS-CoV-2 prevention study during the follow-up were included. Key exclusion criteria were a history of laboratory-confirmed SARS-CoV-2 infection, history of previous SARS-CoV-2 vaccination, receipt of inactivated vaccine 14 days before study enrolment, receipt of live vaccine 28 days before study enrolment, unstable medical conditions, and immunosuppressed individuals. The complete inclusion and exclusion criteria can be found in [Supplementary Methods S1](#).

2.3. Treatment and administration

The S-268019-b (Lot nos. 4841994A, 4841994A-2, K21018, K21020) consisted of a 40 $\mu\text{g}/\text{mL}$ solution of a modified recombinant S-protein produced in rhabdovirus-free insect cells using the baculovirus expression vector system [19] as an antigen and an oil-in-water emulsion, including squalene, tocopherol, and polysorbate 80 as an adjuvant (Lot nos. 4841994B, 4841994B-2, 4841994B-3, 4841994B-4, 1Y02, 2104). The solutions were mixed at a 1:1 ratio. A final volume of 0.5 mL of the mixture containing a 10 μg dose of the S-protein was administered intramuscularly. For the placebo, commercially available 0.9 % (w/v) physiological saline for injection was used. The interventions were administered as two doses at a 28-day interval in the initial and the crossover vaccination period, respectively. Participants were observed for 30 min following vaccination for anaphylactic reactions and any immediate adverse events (AEs).

2.4. Randomisation and blinding

Using an interactive web response system, participants were randomly assigned (2:1) to receive either S-268019-b or placebo at the time of the initial vaccination period. Randomisation was also stratified by age group (18–64 years and ≥ 65 years). The participants,

investigators, sub-investigators, site staff, sponsor, and the sponsor's designees (involved in monitoring, data management, or other study aspects) except persons in charge of management, dispensing and administration of the study interventions were blinded to the interventions. Participants were followed-up, and efficacy and safety data were analysed from the point of unblinding.

2.5. COVID-19 ascertainment, severity, and follow-up

Participants were required to fill in an e-diary/paper diary for recording predefined solicited AEs every day during 7 days after the first and second vaccination. Surveillance of COVID-19-related symptoms was conducted at least once a week; if the participants experienced at least one COVID-19-related symptom (new or worsened), the participants were followed up every day. A participant was defined to have symptomatic COVID-19 if they had both, a positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test result and had at least one of the following COVID-19-related symptoms, including 1) fever (oral temperature $\geq 38.0^\circ\text{C}/100.4^\circ\text{F}$ or axillary temperature $\geq 37.5^\circ\text{C}/99.5^\circ\text{F}$), shortness of breath, difficulty breathing for ≥ 1 day, and/or 2) chills, cough, fatigue, muscle aches, body aches, headache, the new loss of taste or smell, sore throat, congestion, runny nose, nausea, vomiting, diarrhoea for ≥ 2 consecutive days.

Once a participant reported fever, shortness of breath, difficulty breathing or other 13 listed COVID-19 symptoms, the participant then had to visit the study site, or the investigator had to visit the participant's home or place of sojourn immediately (no later than three days) for a potential COVID-19 illness visit to provide a nasopharyngeal swab sample for the SARS-CoV-2 RT-PCR test. The sample was collected during the visit by the investigator. For SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 participants, the investigator scheduled a COVID-19 illness visit (additional site/telehealth visit depending on participant's condition) to perform additional examinations including physical, vital signs, oxygen saturation (SpO_2), and chest X-ray. The participants were further monitored until recovery from COVID-19.

Severe cases of COVID-19 were defined as participants having any of the following conditions: clinical signs at rest indicative of severe systemic illness (respiratory rate = 30 breaths per minute, pulse rate = 125 beats per minute, $\text{SpO}_2 = 93\%$ in room air at sea level, or partial pressure of oxygen to fraction of inspired oxygen ratio [$\text{PaO}_2/\text{FiO}_2$ ratio] < 300 mmHg); respiratory failure (requiring high-flow oxygen, non-invasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation; evidence of shock [systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg, or requiring vasopressors]); significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death.

The COVID-19 follow-up visit was scheduled 28 days after the potential COVID-19 illness visit. If any COVID-19-related symptom persisted during the follow-up visit, the investigator followed up until the participant was fully recovered or was medically stable.

Participants could discontinue after initial vaccination if infected with SARS-CoV-2, based on the RT-PCR test at the potential COVID-19 illness visit. Additional details are provided in [Supplementary Methods S2](#).

2.6. Endpoints and assessments

The primary endpoint was vaccine efficacy evaluated as the incidence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 during the initial vaccination period, with onset at least 14 days following the second dose in seronegative and PCR-negative participants at baseline. Participants who withdrew or were diagnosed with SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 before 14 days following the second dose in the initial vaccination period were excluded from the primary endpoint analysis.

Key secondary endpoints included the incidence of SARS-CoV-2 RT-

PCR-positive severe COVID-19 with onset at least 14 days following the second dose during the initial vaccination period, and the incidence of SARS-CoV-2 RT-PCR-positive symptomatic or severe COVID-19 following the first dose during the initial vaccination period in seronegative and RT-PCR-negative participants at baseline.

Immunogenicity was assessed in a subset of participants by measuring the geometric mean titres (GMT) at each study visit, the geometric mean fold rise (GMFR) of antibody titre versus baseline, and the seroconversion rate (percentage of participants with a ≥ 4 -fold increase in post-vaccination antibody titre from baseline) at each post-vaccination study visit, for the serum levels of ancestral SARS-CoV-2 (Pango lineage A, Wuhan) neutralising antibody and anti-spike protein immunoglobulin G (IgG) antibody. Blood samples were collected from all participants for antibody testing (both anti-SARS-CoV-2 and SARS-CoV-2 S-protein and N-protein) on Day 1 before vaccination. SARS-CoV-2 neutralising antibodies were measured using live virus neutralisation assays, and anti-SARS-CoV-2 S-protein IgG antibodies using chemiluminescence assays.

Safety was assessed as the incidence of treatment-emergent AEs (hereafter referred to as AEs), treatment-related AEs (TRAEs), serious adverse events (SAEs), AEs of special interest (AESIs), medically attended AEs (MAAEs), and measurement of vital signs (body temperature, pulse rate, respiratory rate, blood pressure, and SpO₂). Reactogenicity of S-268019-b was assessed based on reports of predefined solicited local and systemic AEs occurring after the first and second vaccinations and until 7 days post-vaccination. The definitions of the safety and reactogenicity assessments are described in [Supplementary Methods S3](#). The independent data and safety monitoring board reviewed the SAEs on a monthly basis to assess the ongoing suitability.

A certified central laboratory (BML, Inc. and LSI Medience Corporation) performed all the laboratory tests except for RT-PCR tests at baseline. At baseline, the SARS-CoV-2 RT-PCR (qualitative or quantitative) were performed at study sites or local laboratories in accordance with local regulations or institutional standards. The RT-PCR test at the potential COVID-19 illness visit was performed using cobas® SARS-CoV-2 Qualitative Test [20] (Roche Diagnostics, Mannheim, Germany) based on the standard instructions of the manufacturer.

2.7. Statistical analyses

Demographic and baseline characteristics were summarised by the intervention group using summary statistics for the modified intention-to-treat (mITT) population, which included all randomised participants who received at least one dose of the intervention excluding participants who had evidence of past or present SARS-CoV-2 infection at baseline (positive for RT-PCR or IgG antibody against SARS-CoV-2 N-protein).

Two interim analyses to monitor efficacy data by the independent data and safety monitoring board were planned during the initial vaccination period. However, the total target of 66 participants meeting the primary efficacy endpoint was achieved earlier than the expected cut-off date for the interim analysis. Hence, only the primary analysis was performed using the data obtained as soon as the total target cases were accumulated.

As defined in the protocol, the primary endpoint was evaluated on the mITT population and supported by the Per Protocol Set (PPS) analysis, which included all randomised participants in the mITT population and had no major protocol deviations in the initial vaccination period. For the primary efficacy analysis, 66 participants meeting the primary efficacy endpoint definition within the population of participants who were seronegative and PCR-negative at baseline and had not met the criteria for the primary efficacy endpoint within 14 days post-second vaccination was required to demonstrate with at least 90 % power that vaccine efficacy was >30 %. Approximately 54,915 participants were to be randomised, assuming an observed attack rate of 0.5 % per year in participants receiving placebo, 10 % of the unevaluable participants due to dropout and/or baseline seropositive, and 6-month

follow-up of each participant. A Poisson regression model [21] with robust variance, which included age as covariate and the log of the follow-up time as offset, was used to estimate vaccine efficacy (1-relative risk of the primary endpoint among the S-268019-b-group versus the placebo-group during the initial vaccination period). The efficacy was demonstrated if the null hypothesis of vaccine efficacy ≤ 30 % was rejected, i.e., when the lower limit of 95 % confidence interval (CI) of vaccine efficacy was >30 %. Cumulative incidence rates of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 occurring in the initial vaccination period were estimated with the Kaplan-Meier method [22].

The immunogenicity subset were participants enrolled in three investigational sites where additional immunological testing was conducted. The immunogenicity subset included participants selected from all randomised participants in the mITT population with a valid immunogenicity test result before and at least one valid result after the first vaccination. The GMT and GMFR for the SARS-CoV-2 neutralising antibody and anti-spike protein IgG antibody, along with 95 % CI, were summarised by the intervention group. The 95 % CI was calculated based on the *t*-distribution of the log-transformed values for GMT or GMFR, then back-transformed to the original scale for presentation. The GMT ratio was obtained using an analysis of covariance (ANCOVA) model with intervention group as fixed effect and age as covariate. The seroconversion rate was estimated for each intervention group along with the 95 % CI, which was calculated using the Clopper-Pearson method [23].

The safety analysis set (SAS) included all randomised participants receiving at least one intervention dose. The number and percentage (including 95 % CI) of participants with AEs, other SAEs, AESIs, MAAEs, AEs leading to discontinuation of intervention, and death were summarised by intervention group. Numbers and percentages of participants with AEs, TRAEs, and AEs leading to discontinuation of intervention by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) were provided by the intervention group. The number and percentage of participants who presented with solicited local and systemic AEs within 7 days after the first and second vaccinations were tabulated, and severity and summarised by intervention group. Summary statistics for vital signs were summarised by the intervention group.

All analyses were performed using SAS Version 9.4.

2.8. Ethics

The study protocol, informed consent form, and other relevant documents were reviewed and approved by the National Ethics Committee in Biomedical Research under the Ministry of Health. The study was registered with [ClinicalTrials.gov](#) (NCT05212948) and conducted following the principles of the Declaration of Helsinki, Council for International Organisations of Medical Sciences, and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Guidelines.

3. Results

3.1. Participants

Between December 2021 and April 2022, 11,223 participants were screened, after which enrolment was terminated since the target number of cases were reached. Of these, 2,629 participants did not meet the eligibility criteria ([Fig. 1b](#)). Hence, 8,594 participants (S-268019-b: N = 5,727; placebo N = 2,867) were randomised. Participant recruitment was stopped earlier than planned due to the major outbreak of the Omicron variant in Vietnam, and the targeted number of COVID-19 events was observed by the end of March 2022. Here, we report results only up to the data cut-off date from the initial vaccination period.

As of data cut-off date 31 March 2022, the mITT population, immunogenicity subset, and SAS population included 7,889 (S-268019-

Table 1
Demographic and baseline characteristics of participants (mITT population).

Categories	S-268019-b (N = 5,256)	Placebo (N = 2,633)
Age (years), n	5,256	2,633
Mean (SD)	40.6 (15.5)	40.7 (15.6)
Median (Minimum-Maximum)	38.0 (18–98)	38.0 (18–91)
Age categories (Years), n (%)		
<30	1518 (28.9)	788 (29.9)
≥30–<40	1266 (24.1)	592 (22.5)
≥40–<50	959 (18.2)	469 (17.8)
≥50–<60	92 (15.1)	425 (16.1)
≥60–<65	328 (6.2)	168 (6.4)
≥65	393 (7.5)	191 (7.3)
Height (cm), n	5,255	2,632
Mean (SD)	157.88 (8.62)	157.48 (8.77)
Weight (kg), n	5,255	2,632
Mean (SD)	55.26 (9.15)	55.01 (9.03)
Body Mass Index (kg/m²), n	5,255	2,632
Mean (SD)	22.136 (3.000)	22.172 (3.271)
Sex, n (%)		
Male	3,594 (68.4)	1,732 (65.8)
Female	1,662 (31.6)	901 (34.2)
Ethnicity, n (%)		
Not Hispanic or Latino	5,230 (99.5)	2,617 (99.4)
Hispanic or Latino	16 (0.3)	5 (0.2)
Not reported	10 (0.2)	10 (0.4)
Unknown	0	1 (0.0)
Race, n (%)		
Asian	5,248 (99.8)	2,626 (99.7)
Black or African American	0	1 (0.0)
American Indian or Alaska Native	1 (0.0)	0
Native Hawaiian or Other Pacific Islander	0	0
White	0	0
Not Reported	7 (0.1)	6 (0.2)
Unknown	0	0
Smoking, n (%)		
Yes	2,126 (40.4)	1,029 (39.1)
No	3,130 (59.6)	1,604 (60.9)

The mITT population included all randomised participants who received at least one dose of the study intervention and were seronegative (RT-PCR negative) for SARS-CoV-2 at baseline.

cm, centimetre; kg, kilogram; kg/m², kilogram per metre square; mITT, modified intention-to-treat population; n (%), number (percentage) of participants in each category; N, total number of participants; S-268019-b, recombinant protein modified from S-protein of SARS-CoV-2 (S-910823) mixed in 1:1 ratio with an oil-in-water emulsion (A-910823); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

b: N = 5,256; placebo: N = 2,633), 98 (S-268019-b: N = 64; placebo N = 34), 8,562 (S-268019-b: N = 5,710; placebo N = 2,852) participants, respectively. The proportion of participants that received both doses of the intervention during the initial vaccination period was similar across groups (S-268019-b: 4,539 [79.5 %]; placebo 2,274 [79.7 %]) (Fig. 1b). Common reasons for study discontinuation were physician's decision (S-268019-b: 82 [1.4]; placebo: 48 [1.7]) followed by participant withdrawal (S-268019-b: 72 [1.3]; placebo: 40 [1.4]).

The baseline demographic characteristics were similar between the two groups. Among the 7,889 participants in the mITT population, the majority were male (S-268019-b: 68.4 %; placebo: 65.8 %). The median age of the participants was 38.0 years in both groups. The mean body mass index (standard deviation; SD) was 22.136 (3.000) in the S-268019-b group and 22.172 (3.271) in the placebo group (Table 1). The distribution of participants in each age group was similar between the two groups. Majority of the participants were <40 years of age (Table 1).

3.2. Efficacy

3.2.1. Primary endpoint

The incidence rate (95 % CI) of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 with onset at least 14 days following the second vaccination was 776.41/1,000 person-years (682.04–880.19) in the S-268019-b group and 1272.87/1,000 person-years (1101.32–1463.57) in the placebo group. Compared with placebo, the vaccine efficacy was 39.1 % (26.6–49.5) and did not meet the pre-defined efficacy threshold

of the lower limit of 95 % CI > 30 % (one-sided P = 0.0723; Table 2). The cumulative incidence rates from 14 days after second vaccination are shown in Fig. 2a. Similar results for vaccine efficacy were observed in the PPS population (Supplementary Table S1).

3.2.2. Key secondary endpoints

The incidence rate (95 % CI) of SARS-CoV-2 RT-PCR-positive severe COVID-19 with onset at least 14 days following the second vaccination was 0.00/1,000 person-years (0.00–11.31) in the S-268019-b group and 6.06/1,000 person-years (0.15–33.75) in the placebo group; the vaccine efficacy was 100.0 % (95 % CI non-estimable). As a post-hoc analysis, it was identified that the incidence rate of COVID-19 hospitalisations with onset at least 14 days following the second vaccination during initial vaccination period was 3.07/1,000 person-years (0.08–17.09) in the S-268019-b group and 18.18/1,000 person-years (3.75–53.14) in the placebo group. (Supplementary Table S2). The cumulative incidence rates from initial vaccination are shown in Fig. 2b.

The incidence rate (95 % CI) of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 following the first vaccination was 422.01/1,000 person-years (379.77–467.67) in the S-268019-b group and 608.34/1,000 person-years (536.90–686.63) in the placebo group and the vaccine efficacy was 30.6 % (19.0–40.6). The incidence rate of SARS-CoV-2 RT-PCR-positive severe COVID-19 following the first vaccination was 0.00/1,000 person-years (0.00–4.19) in the S-268019-b group, and 2.25/1,000 person-years (0.06–12.55) in the placebo group (Supplementary Table S3).

Table 2

Vaccine efficacy in SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 with onset at least 14 days following the second vaccination and other efficacy endpoints (mITT population).

	S-268019-b (N = 5,256)	Placebo (N = 2,633)
SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 with onset at least 14 days following the second vaccination		
Participants at risk	3,542	1,790
Participants with RT-PCR-positive symptomatic COVID-19	244	197
Duration (person-years)	314.27	154.77
Incidence rate per 1,000 person-years (95 %CI; LL, UL ^[a])	776.41 (682.04–880.19)	1272.87 (1101.32–1463.57)
Vaccine efficacy versus placebo (%) (95 %CI; LL, UL ^[b])	39.1 (26.6–49.5)	
One-sided P-value ^c	0.0723	
SARS-CoV-2 RT-PCR-positive severe COVID-19 with onset at least 14 days following the second vaccination		
Participants at risk	3,559	1,810
Participants with RT-PCR-positive severe COVID-19	0	1
Duration (person-years)	326.14	165.10
Incidence rate per 1,000 person-years (95 %CI; LL, UL ^[a])	0.00 (0.00–11.31)	6.06 (0.15–33.75)
Vaccine efficacy versus placebo (%) (95 %CI; LL, UL ^[b])	100 (–)	
One-sided P-value ^c	–	
Hospitalised COVID-19 with onset at least 14 days following the second vaccination		
Participants at risk	3,559	1,810
Participants with hospitalized COVID-19	1	3
Duration (person-years)	326.10	164.99
Incidence rate per 1,000 person-years (95 %CI; LL, UL ^[a])	3.07 (0.08–17.09)	18.18 (3.75–53.14)
Vaccine efficacy versus placebo (%) (95 %CI; LL, UL ^[b])	83.2 (–61.5–98.2)	
One-sided P-value ^c	0.1084	
SARS-CoV-2 RT-PCR-positive symptomatic COVID-19		
Participants at risk	5,256	2,633
Participants with RT-PCR-positive symptomatic COVID-19	364	262
Duration (person-years)	862.53	430.68
Incidence rate per 1,000 person-years (95 %CI; LL, UL ^[a])	422.01 (379.77–467.67)	608.34 (536.90–686.63)
Vaccine efficacy versus placebo (%) (95 %CI; LL, UL ^[b])	30.6 (19.0–40.6)	
One-sided P-value ^c	0.4547	
SARS-CoV-2 RT-PCR-positive severe COVID-19		
Participants at risk	5256	2633
Participants with RT-PCR-positive severe COVID-19	0	1
Duration (person-years)	880.24	444.08
Incidence rate per 1,000 person-years (95 %CI; LL, UL ^[a])	0.00 (0.00–4.19)	2.25 (0.06–12.55)
Vaccine efficacy versus placebo (%) (95 %CI; LL, UL ^[b])	100 (–)	
One-sided P-value ^c	–	

The mITT population included all randomised participants who received at least one dose of the study intervention and were seronegative (RT-PCR negative) for SARS-CoV-2 at baseline.

95 % CI, 95 % confidence interval; COVID-19, coronavirus disease 2019; LL, lower limit of the CI; mITT, modified intention-to-treat population; N, total number of participants; RT-PCR, reverse transcriptase-polymerase chain reaction; S-268019-b, recombinant protein modified from S-protein of SARS-CoV-2 (S-910823) mixed in 1:1 ratio with an oil-in-water emulsion (A-910823); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UL, upper limit of the CI.

^a The 95 % CI was constructed using the exact method assuming Poisson distribution.

^b Vaccine efficacy was calculated with its 95 % CI as 1 minus the relative risk (S-268019-b versus placebo) estimated using a Poisson regression model with robust error variance, which included the intervention group, baseline age (continuous) as factors as well as the log of the follow-up time as an offset.

^c One-sided P-value was calculated to test the null hypothesis that the vaccine efficacy ≤ 30 %.

The age-subgrouped vaccine efficacy (95 % CI) against SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 with onset at least 14 days following the two-dose vaccination was higher in the 18–64 years age group at 39.7 % (27.0–50.2) compared to ≥ 65 years age group at 25.6 % (–79.6–69.2).

3.3. Immunogenicity

In the immunogenicity subset, the SARS-CoV-2 neutralising antibody GMTs increased in the S-268019-b group on Days 29 and 57; however, it remained unchanged in the placebo group. The GMTs at baseline and Day 57 were 2.50 (95 % CI non-estimable) and 34.66 (95 % CI: 27.04–44.41) in the S-268019-b group, and 2.50 (95 % CI non-estimable) and 2.69 (95 % CI: 2.31–3.14) in the placebo group,

respectively (Supplementary Table S4), corresponding to a higher GMFR (95 % CI) of 13.86 (10.82–17.76) in the S-268019-b group than in the placebo group (1.08 [0.92–1.25]) on Day 57. Also, on Day 57, the seroconversion rate (95 % CI) for the SARS-CoV-2 neutralising antibody was higher in the S-268019-b group (93.1 % [83.3–98.1]) versus the placebo group (3.6 % [0.1–18.3]).

The GMTs for the anti-spike protein IgG increased in the S-268019-b group on Days 29 and 57; however, it remained unchanged in the placebo group. The GMTs (95 % CI) at baseline and Day 57 were 3.72 (3.43–4.04) and 25209.25 (17163.57–37026.44) in the S-268019-b group, and 4.27 (3.50–5.21) and 6.39 (3.10–13.19) in the placebo group, respectively (Supplementary Table S4), corresponding to a higher GMFR of 6710.95 (4556.29–9884.54) in the S-268019-b group than in the placebo group (1.46 [0.75–2.85]) on Day 57. The

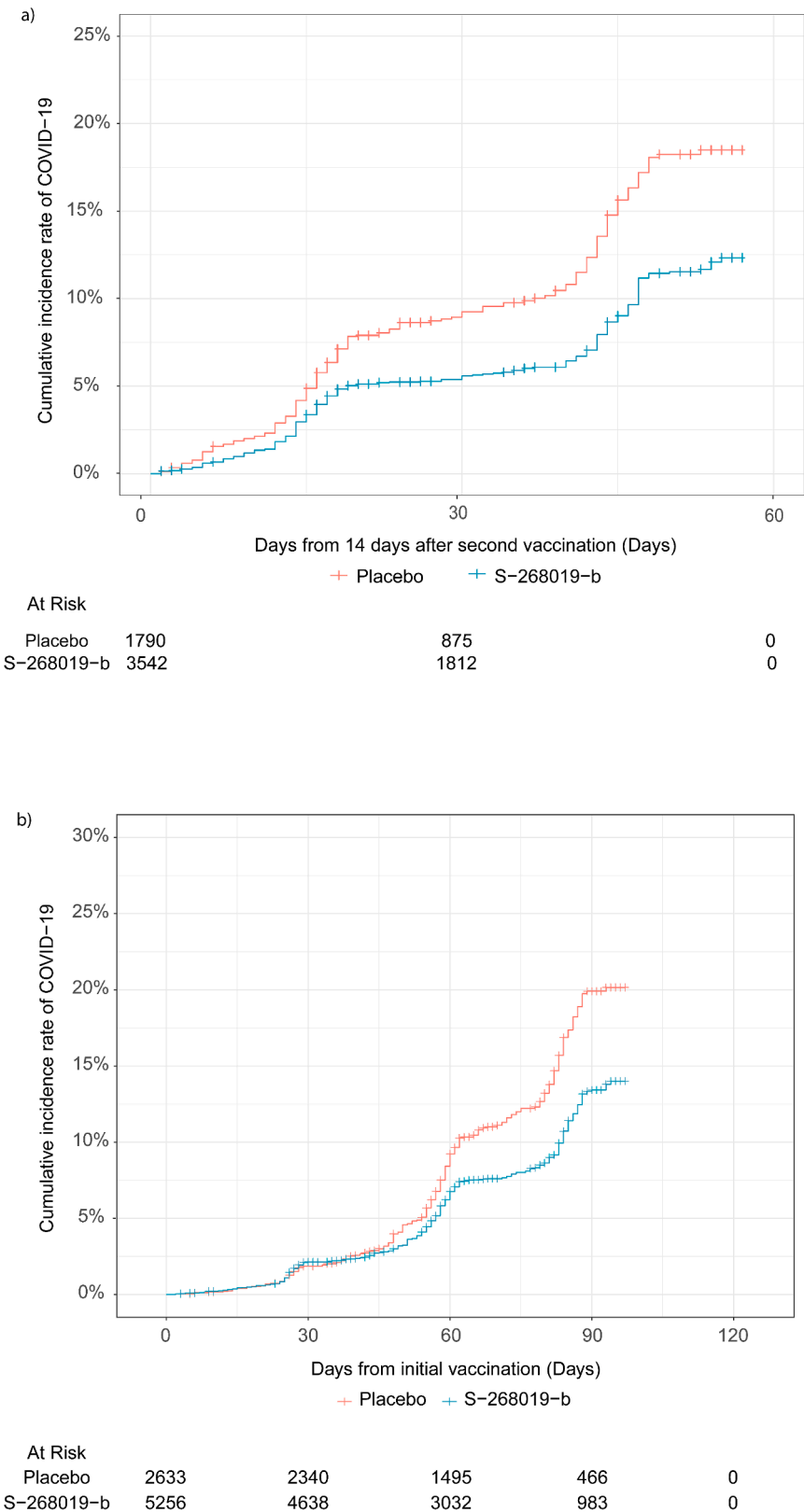


Fig. 2. Kaplan-Meier curve for the cumulative incidence rates of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 (mITT population). The cumulative incidence rate shown are from (a) 14 days after second vaccination (b) initial vaccination. The mITT population included all randomised participants who received at least one dose of the study intervention and were seronegative (RT-PCR negative) for SARS-CoV-2 at baseline. COVID-19, coronavirus disease 2019; mITT, modified intention-to-treat population; RT-PCR, reverse transcriptase-polymerase chain reaction; S-268019-b, recombinant protein modified from S-protein of SARS-CoV-2 (S-910823) mixed in 1:1 ratio with an oil-in-water emulsion (A-910823); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3
Overall summary of adverse events* (SAS population).

	S-268019-b (N = 5,710)			Placebo (N = 2,852)		
	n (%)	95 % CI		n (%)	95 % CI	
		LL	UL		LL	UL
Adverse events	2,700 (47.3)	46.0	48.6	941 (33.0)	31.3	34.8
Other serious AEs	13 (0.2)	0.1	0.4	21 (0.7)	0.5	1.1
AEs leading to discontinuation	7 (0.1)	0.0	0.3	12 (0.4)	0.2	0.7
AESI	7 (0.1)	0.0	0.3	2 (0.1)	0.0	0.3
MAAEs	29 (0.5)	0.3	0.7	27 (0.9)	0.6	1.4
Deaths	4 (0.1)	0.0	0.2	3 (0.1)	0.0	0.3

The SAS population included all randomised participants receiving at least one dose of the intervention. 95 % CI, 95 % confidence interval; AEs, adverse events; AESIs, AEs of special interest; n (%), number (percentage) of participants in each category; N, total number of participants; LL, lower limit of the CI; MAAEs, medically attended AEs; mITT, modified intention-to-treat population; S-268019-b, recombinant protein modified from S-protein of SARS-CoV-2 (S-910823) mixed in 1:1 ratio with a squalene-in-water emulsion (A-910823); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAS, safety analysis set; UL, upper limit of the CI.

* The safety analyses were based on treatment-emergent AEs (referred to as AEs).

Table 4
Incidence of adverse events* and treatment-related adverse events (≥5 % incidence rate between treatment groups) by SOC and PT (SAS population).

System Organ Class Preferred Term	S-268019-b (N = 5,710) n (%)	Placebo(N = 2,852) n (%)
Adverse events		
General disorders and administration site conditions	2,303 (40.3)	624 (21.9)
Injection site pain	1,942 (34.0)	340 (11.9)
Fatigue	1,098 (19.2)	367 (12.9)
Nervous system disorders	969 (17.0)	343 (12.0)
Headache	958 (16.8)	333 (11.7)
Musculoskeletal and connective tissue disorders	828 (14.5)	201 (7.0)
Myalgia	826 (14.5)	200 (7.0)
Treatment-related adverse events		
General disorders and administration site conditions	2,227 (39.0)	579 (20.3)
Injection site pain	1,903 (33.3)	332 (11.6)
Fatigue	1,051 (18.4)	339 (11.9)
Nervous system disorders	894 (15.7)	303 (10.6)
Headache	893 (15.6)	303 (10.6)
Musculoskeletal and connective tissue disorders	794 (13.9)	184 (6.5)
Myalgia	793 (13.9)	184 (6.5)

The SAS population included all randomised participants receiving at least one dose of the intervention.

n (%), number (percentage) of participants in each category; N, total number of participants; PT, preferred term; S-268019-b, recombinant protein modified from S-protein of SARS-CoV-2 (S-910823) mixed in 1:1 ratio with a squalene-in-water emulsion (A-910823); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAS, safety analysis set; SOC, system organ class.

* The safety analyses were based on treatment-emergent AEs (referred to as AEs).

seroconversion rate (95 % CI) for the SARS-CoV-2 anti-spike protein IgG antibody on Day 29 was 100.0 % (94.2–100.0) in the S-268019-b group and 0.0 % (0.0–10.9) in the placebo group. Similarly, on Day 57, the seroconversion rate was 98.2 % (90.6–100.0) and 7.1 % (0.9–23.5) in the S-268019-b and placebo groups, respectively.

3.4. Safety

3.4.1. AEs and TRAEs

A total of 8,463 AEs were reported in 47.3 % (95 % CI: 46.0–48.6) of participants in the S-268019-b group, and 2,288 AEs in 33.0 % (95 % CI: 31.3–34.8) of participants in the placebo group (Table 3). AEs with an incidence of ≥5 % difference between the intervention groups were injection site pain (S-268019-b: 34.0 %; placebo: 11.9 %), fatigue (S-268019-b: 19.2 %; placebo: 12.9 %), headache (S-2168019-b: 16.8 %;

placebo: 11.7 %), and myalgia (S-268019-b: 14.5 %; placebo: 7.0 %) (Table 4). Most AEs were of Grade 1 intensity (S-268019-b: 38.4 % participants; placebo: 25.7 % participants). The occurrence of Grade 2 and Grade 3 AEs was low. The most frequently reported Grade 3 AEs included blood pressure increased (n = 24), pyrexia (n = 20), hypertension (n = 15) in the S-268019-b group, and increased blood pressure (n = 17) in the placebo group. There were no reports of Grade 4 AEs during the study.

A total of 7,528 TRAEs were reported in 42.4 % (95 % CI: 41.1–43.7) of participants in the S-268019-b group, and 1,788 TRAEs in 26.4 % (95 % CI: 24.8–28.1) of participants in the placebo group. The TRAEs with an incidence of ≥5 % difference between the intervention groups were injection site pain, fatigue, headache, and myalgia (Table 4). Similar to the overall AEs, most TRAEs were of Grade 1 intensity, and the occurrence of Grade 2 and Grade 3 TRAEs was low. The most frequent Grade 3 TRAE was pyrexia (n = 19) in the S-268019-b group. There were no reports of Grade 4 or Grade 5 events.

3.4.2. Non-fatal SAEs and AEs leading to discontinuation of intervention

The proportion of participants with SAEs and AEs leading to study discontinuation was low (Table 3). A total of 13 non-fatal SAEs were reported in 0.2 % (95 % CI: 0.1–0.4) of participants in the S-268019-b group and 25 events in 0.7 % (95 % CI: 0.5–1.1) in the placebo group (Table 3). All SAEs were considered unrelated to S-268019-b. A total of 7 AEs leading to discontinuation of intervention were reported in 0.1 % (95 % CI: 0.0–0.3) of participants in the S-268019-b group, and 12 AEs in 0.4 % (95 % CI: 0.2–0.7) of participants in the placebo group (Table 3). In the S-268019-b group, meningioma, epilepsy, blurred vision (Grade 1, and considered related to the intervention), tachycardia, hypertension, death, and hepatic enzyme increased were reported by one participant each. In the placebo group, pneumonia, cervix carcinoma, cachexia, hepatic encephalopathy, hypotension, asthma, spontaneous abortion, asthenia, and hepatic enzyme increased were reported by one participant each (Supplementary Table S5). In the S-268019-b group, one participant reported COVID-19 and in the placebo group 3 participants reported COVID-19 (Supplementary Table S6).

3.4.3. AESIs and MAAEs

A total of 7 and 3 AESIs were reported in 0.1 % (95 % CI: 0.0–0.3) participants each in the S-268019-b and placebo groups, respectively (Table 3). A total of 2 treatment-related AESIs (Grade 1 injection site pain and heart rate increase) were reported in the S-268019-b group, while no treatment-related AESI was reported in the placebo group. All treatment-related AESIs were of Grade 1 severity.

A total of 31 and 44 MAAEs were reported in 0.5 % (95 % CI: 0.3–0.7) and 0.9 % (95 % CI: 0.6–1.4) of participants in the S-268019-b and placebo groups, respectively (Table 3). Three treatment-related

MAAEs were reported in the S-268019-b group and 1 in the placebo group, which were either of Grade 2 or Grade 3 severity.

3.4.4. Deaths

A total of 4 deaths in the S-268019-b group (0.1 % [95 % CI: 0.0–0.2]; completed suicide, meningioma, craniocerebral injury, death) and 3 in the placebo groups (0.1 % [95 % CI: 0.0–0.3]; cachexia, hepatic encephalopathy, pneumonia) were reported, and none were considered related to S-268019-b or placebo (Table 3). There were no COVID-19 related deaths in this study.

3.4.5. Solicited systemic and local AEs

A total of 4,353 and 1,368 solicited systemic AEs were reported in 29.8 % (95 % CI: 28.7–31.0) and 20.5 % (19.0–22.0) of participants in the S-268019-b and placebo groups, respectively. A total of 4,223 and 1,312 treatment-related solicited systemic AEs were reported in 29.1 % (27.9–30.3) and 19.9 % (18.5–21.4) of participants in the S-268019-b and placebo groups, respectively. After the first vaccination, the most frequently reported treatment-related systemic AEs were fatigue (12.1 %) followed by myalgia (10.4 %) in the S-268019-b group, and fatigue (8.2 %) followed by headache (7.9 %) in the placebo group (Supplementary Table S7). After the second vaccination, the most frequently reported treatment-related systemic AEs were fatigue (12.8 % and 6.8 %) followed by headache (10.5 % and 5.2 %) in the S-268019-b and placebo groups, respectively. The incidence of fever was low in both groups (S-268019-b: 5.0 %; placebo: 1.7 %). (Supplementary Table S7).

A total of 3,243 and 406 solicited local AEs were reported in 34.6 % (95 % CI: 33.4–35.9) and 12.2 % (11.0–13.4) of participants in the S-268019-b and placebo groups, respectively. A total of 3,152 and 394 treatment-related solicited systemic AEs were reported in 34.0 % (32.7–35.2) and 11.9 % (10.7–13.1) of participants in the S-268019-b and placebo groups, respectively. In both intervention groups, pain was the most frequently reported treatment-related solicited local AE after both vaccinations (Supplementary Table S7).

Most systemic and local AEs were of Grade 1 or Grade 2 severity following both vaccinations. After the first vaccination, all Grade 3 solicited systemic and local AEs, except for fatigue ($n = 1$) in the S-268019-b group, were treatment-related. After the second vaccination, Grade 3 solicited systemic AEs, including fever ($n = 13$), fatigue ($n = 2$), and diarrhoea ($n = 1$) in the S-268019-b group, and fever ($n = 3$) in the placebo-group, and all Grade 3 local AEs were treatment-related.

3.5. Vital signs

The mean systolic/diastolic blood pressure, pulse rate, respiratory rate, and body temperature data were similar across both groups across all time points, with no abnormal findings.

4. Discussion

This was a phase 3 study to evaluate the clinical efficacy and safety of the two-dose regimen of S-268019-b (10 µg dose, 28 days apart) against SARS-CoV2 in Vietnamese participants which was conducted during the Omicron (BA.2)-dominant period. Overall, the vaccine efficacy against SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 did not reach the pre-defined efficacy threshold criteria since the lower limit of the 95 % CI did not exceed 30 %. The results are consistent with observations for other vaccines in real-world studies, which had lower effectiveness against emergent variants of SARS-CoV-2 [24]. Similarly, efficacy against severe COVID-19 was 100 %, as with Moderna's mRNA-1273 vaccine [25]. With regards to immunogenicity results, in our study, we observed a clear increase in the GMTs and GMFRs for the SARS-CoV-2 neutralising antibody and anti-spike protein IgG following immunisation with S-268019-b. Safety and reactogenicity observations showed S-268019-b to be well tolerated in adult Vietnamese participants.

S-268019-b was designed for prevention against ancestral strains of

SARS-CoV-2; the vaccine efficacy of S-268019-b during the Omicron (BA.2)-dominant period was 39.1 %. This study was planned and conducted during the Delta period. However, the Omicron variant rapidly became the dominant strain soon after the trial initiation. An ongoing systematic review of the effectiveness of primary series of COVID-19 mRNA vaccines has demonstrated that the efficacy for most of these vaccines against symptomatic disease was predominantly below the 50 % threshold for efficacy during the Omicron-dominant period, despite their efficacy being much higher against the previous variants and the ancestral strain. One of the few prospective studies conducted during the Omicron (B.1.1.529)-dominant period, a phase 2–3, randomised, placebo-controlled study of mRNA-1273 (SPIKEVAX®) vaccine in young children (6 months to 5 years of age), estimated the vaccine efficacy to be 36.8 % (95 % CI: 12.5–54.0) in children aged 2–5 years and 50.6 % (95 % CI: 21.4–68.6) among those aged 6–23 months old [26]. Also, it is hypothesized that the neutralizing antibody titre of COVID-19 vaccines correlates with their efficacy against COVID-19 [27]. Studies have reported lower efficacy and effectiveness against variants especially, the omicron variant. A serosurveillance in Hong Kong during an outbreak of Omicron demonstrated that the VE of BNT162b2 and CoronaVac after 3 or 4 doses were substantially lower against Omicron infection 7 days after vaccination. BNT162b2: (VE of 48 % (95 % credible interval 34–64 %) and 69 % (46–98 %); CoronaVac: VE of 30 % (1–66 %) and 56 % (6–97 %). There was a sharp drop in efficacy at 100 days for both vaccines, during this period. BNT162b2: 26 % (7–41 %) and 35 % (10–71 %); CoronaVac: 6 % (0–29 %) and 11 % (0–54 %) [28]. Similarly, primary vaccination with ChAdOx1 and BNT162b2 did not provide protection against symptomatic disease in a British cohort although booster vaccination with either ChAdOx1, BNT162b2, mRNA after primary course with ChAdOx1 or BNT162b2 offered protection which was seen to wane over time [29]. In populations exposed to a mix of variants, it is challenging to assess the vaccine efficacy since natural immunity cannot be differentiated from vaccine induced immunity. Furthermore, capsular switch of the virus due to unhindered transmission enables it to evade the immune mechanism. The change in the structure of the viral envelop creates a different epitope against which the vaccine antigen may be incapable of inducing a strong immune response.

The immunogenicity of S-268019-b as a primary series was superior to AZD1222, whose efficacy against symptomatic COVID-19 during the ancestral strain circulation period was 62.1 % [30]. Furthermore, the geometric mean titre of neutralizing antibody against Omicron variant BA.2 after S-268019-b primary series measured in another study was about 20 times lower than that against the ancestral SARS-CoV-2 [31]. Additionally, it has been observed that the vaccine-induced cellular immunity with S-268019-b was similar to that with ChAdOx1 nCoV-19 [31]. Cellular immunity is thought to be important in preventing severe COVID-19 disease and prevents wider range of variant infection than neutralizing antibodies [32]. This may possibly contribute to the finding that S-268019-b had a potential for reduction of hospitalization during Omicron (BA.2) dominant period. Given that the neutralizing antibody is considered a correlate of protection and these data taken together suggest that the efficacy of S-268019-b might have been much higher than 40 % if the trial had been performed during the Delta or the earlier period. However, in reality, and in line with the reported vaccine efficacy of the primary vaccination with ancestral S protein against Omicron variants, the efficacy of S-268019-b could also be limited in the Omicron period [24,28,29].

Additionally, the incidence of SARS-CoV-2 RT-PCR-positive severe COVID-19 or COVID-19 requiring hospitalisation was numerically low following vaccination with S-268019-b. This signifies that S-268019-b has favourable potential for preventing severe symptoms or hospitalisation related to COVID-19 in Vietnamese adults. Nevertheless, it is to be noted that in all cases of vaccine efficacy against severe COVID-19 and preventing hospitalisations, the 95 % CIs were wide or could not be calculated due to the small number of cases. Hence, caution must be exercised when interpreting these results, although it was assumed that

such effects could be expected.

There were no significant safety concerns regarding S-268019-b. In our study, injection site pain, fatigue, headache, and myalgia were commonly reported AEs and were similar to those previously reported in the clinical trials for S-268019-b [16,18]. Although 7 deaths were reported in the study, none were considered related to the interventions. Similar to the study by Anderson et al., Grade 3 solicited systemic and local AEs were rare with S-268019-b but slightly more frequent following the second vaccination [33]. Notably, in the current study the incidence of fever was low with S-268019-b (5.0 %) [16]. Overall, safety findings were consistent with observations in previously published S-268019-b trials and another prospective study during the Omicron-dominant period [5,18,31].

This is the first study of S-268019-b evaluating efficacy for preventing symptomatic COVID-19 during the Omicron (BA.2)-dominant period in Vietnam. The number of COVID-19 events for the primary efficacy analysis was obtained within the data cut-off date. However, there are some limitations to the study. The incidences of SARS-CoV-2 infections and COVID-19 were assessed to evaluate the vaccine efficacy during the Omicron (BA.2)-dominant period. Participant enrolment started on 25 December 2021; however, as of 24 December 2021, 65,354,960 adults (≥ 18 years of age) had received the 2nd dose of the COVID-19 vaccine with ~ 90 % coverage rate. This likely affected the transmission of SARS-CoV-2 in the study population and prevented the spread of the ancestral strains. Additionally, the antigenic mismatch against the Omicron variant reduced the immune response to the vaccine. Factors like ethnic diversity, underrepresentation of female participants in the study and lower number of elderly people should be considered while interpreting the results from this study.

To conclude, the S-268019-b prevented symptomatic COVID-19 in the Vietnamese population during the Omicron (BA.2)-dominant period with a similar prevention rate to other vaccines using S-protein of the ancestral SARS-CoV2 strain, and also appears to protect against severe COVID-19. Despite not achieving the targeted efficacy threshold, the findings are promising for a novel approach to protect against COVID-19 variants. The crossover vaccination period of the study is currently ongoing, and an exploratory analysis assessing the durability of vaccine efficacy during this period and determination of the nucleotide sequences of SARS-CoV-2 variants in the participants diagnosed with COVID-19 is expected to provide further insights regarding the efficacy of S-268019-b. These findings will add to the medically important growing evidence against vaccines to prevent infectious variants of SARS-CoV-2. If S-268019-b is approved, together with public health measures advocated by the Vietnamese health authorities, its use could help reduce the public health burden due to COVID-19 and its variants.

Author contributions

HF, YI, MA and TS contributed to conceptualisation. MS and YI contributed to data curation and validation. AK and YT contributed to formal analysis. All authors contributed to data interpretation. MA contributed to funding acquisition and project administration. VDT, PTVA, CVM and DTH contributed to investigation. VDT and MA contributed to supervision. All authors contributed to revision and editing the draft manuscript. All authors read and approved the final version of the manuscript.

Conflicts of interest

AK, YT, HF, YI, MA, and TS are employees of Shionogi & Co., Ltd., and TS and YT own stock options in the Company.

AJP: received grants paid to the institution from Gates Foundation, Wellcome Trust, CEPI, MRC, NIHR, Serum Institute of India, Astra Zeneca, and EC, is a contributor to intellectual property licensed by Oxford University Innovation to AstraZeneca, received consulting fees from Shionogi & Co., Ltd., and was honorary Chair of DHSC's Joint

Committee on Vaccination and Immunisation and member of WHO's SAGE until 2022.

VDT: Received fees from Shionogi & Co., Ltd., to conduct the clinical trial.

The other authors do not have any conflict of interest to disclose.

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CRediT authorship contribution statement

Vu Dinh Thiem: Writing – review & editing, Supervision, Investigation. **Pham Thi Van Anh:** Writing – review & editing, Investigation. **Chu Van Men:** Writing – review & editing, Investigation. **Do Thai Hung:** Writing – review & editing, Investigation. **Andrew J. Pollard:** Writing – review & editing. **Akari Kamitani:** Writing – review & editing, Formal analysis. **Yukio Tada:** Writing – review & editing, Formal analysis. **Hidenori Fukuyama:** Writing – review & editing, Conceptualisation. **Yuka Iwasaki:** Writing – review & editing, Validation, Data curation, Conceptualisation. **Mari Ariyasu:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualisation. **Takuhiro Sonoyama:** Writing – review & editing, Conceptualisation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Vu Dinh Thiem reports financial support was provided by Shionogi & Co., Ltd. Andrew J Pollard reports financial support was provided by Gates Foundation, Wellcome Trust, Cepi, MRC, NIHR, Serum Institute of India, Astra Zeneca, and EC. Andrew J. Pollard reports financial support was provided by Shionogi and Co Ltd. Akari Kamitani reports a relationship with Shionogi and Co Ltd that includes: employment. Yukio Tada reports a relationship with Shionogi and Co Ltd that includes: employment and equity or stocks. Hidenori Fukuyama reports a relationship with Shionogi and Co Ltd that includes: employment. Yuka Iwasaki reports a relationship with Shionogi and Co Ltd that includes: employment. Mari Ariyasu reports a relationship with Shionogi and Co Ltd that includes: employment. Takuhiro Sonoyama reports a relationship with Shionogi and Co Ltd that includes: employment and equity or stocks. Andrew J Pollard is a contributor to intellectual property licensed by Oxford University Innovation to AstraZeneca and was honorary Chair of DHSC's Joint Committee on Vaccination and Immunisation and member of WHO's SAGE until 2022. Pham Thi Van Anh, Chu Van Men, and Do Thai Hung have no conflicts to declare. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets analysed in this study are available on reasonable request of researchers through the clinical study data request platform (<https://vivli.org/>) after the researchers and SHIONOGI Group enter into a contract (which will have certain requirements with respect to personal data privacy, confidentiality, and compliance with the law).

For further details, please refer to the websites of Shionogi & Co., Ltd.

(<https://www.shionogi.com/shionogi/global/en/company/policies/shionogi-group-clinical-trial-data-transparency-policy.html>).

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2024.04.084>.

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