2. SYNOPSIS

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Study Title:
A Phase 3, Randomized, Observer-Blind, Placebo-Controlled Cross-over Study to Evaluate the Efficacy, Safety, and Immunogenicity of S-268019 for the Prevention of COVID-19

Investigators and Study Centers: This study was a multicenter study conducted at 24 sites in Vietnam.

Publication (reference): Not applicable

Studied Period:
Initiated on 25 Dec 2021 (Date first participant signed informed consent)
Completed on 19 Jul 2023 (Date of last participant's last visit)

Phase of Development: Phase 3

Objectives, Estimands and Endpoints:

Objectives	Estimands/Endpoints
Primary	
● To assess the efficacy of a 2-dose regimen of S-268019-b for the prevention of COVID-19 in the Initial Vaccination Period prior to crossover in participants without evidence of infection before vaccination as compared to placebo.	● **Population:** Modified Intent-to-Treat (mITT) population
	● **Endpoint:** The first occurrence of SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR)-positive symptomatic COVID-19 in the Initial Vaccination Period (ie, prior to crossover), with onset at least 14 days following the second vaccination in participants seronegative and PCR-negative at baseline.
	● **Intercurrent events:** For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint, the absence of data following these participants' withdrawal was treated as missing; participants who withdrew before 14 days post second vaccination or who were diagnosed with SARS-CoV-2 infection prior to 14 days post second vaccination in the Initial Vaccination Period were excluded from the primary endpoint analysis.
	● **Summary measure:** Vaccine efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the intervention group

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	relative to the incidence of infection in the control group.)
Key Secondary	
● To assess the efficacy of S-268019-b for the prevention of symptomatic infection of COVID-19 as compared to placebo.	● The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 in the Initial Vaccination Period with onset at least 14 days following the second vaccination in participants seronegative and PCR-negative at baseline.
	● The first occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 in the Initial Vaccination Period in participants seronegative and PCR-negative at baseline.
	● The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 in the Initial Vaccination Period in participants seronegative and PCR-negative at baseline.
Secondary	
● To assess the efficacy of S-268019-b for the prevention of symptomatic infection of COVID-19 as compared to placebo.	● The first occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 in the Initial Vaccination Period with onset at least 14 days following the second vaccination in participants regardless of serostatus or PCR status at baseline.
	● The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 in the Initial Vaccination Period with onset at least 14 days following the second vaccination in participants regardless of serostatus or PCR status at baseline.
	● The first occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 in the Initial Vaccination Period in participants regardless of serostatus or PCR status at baseline.
	● The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 in the Initial Vaccination Period in participants regardless of serostatus or PCR status at baseline.
● To assess the efficacy of a 2-dose regimen of S-268019-b for the prevention of asymptomatic infection of COVID-19 in participants without evidence of infection before vaccination.	● The first occurrence of asymptomatic SARS-CoV-2 infection in the Initial Vaccination Period beginning 14 days following the second vaccination in participants seronegative and PCR-negative at baseline. Antibodies to SARS-CoV-2 N-protein were used to determine natural infection and to determine the incidence of

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	asymptomatic infection acquired during study follow-up.
● To assess the safety and reactogenicity of S-268019-b.	● The incidence of adverse events (AEs), treatment-related AEs, serious adverse events (SAEs), adverse events of special interest (AESIs), medically attended adverse events (MAAEs), solicited local AEs, and solicited systemic AEs, and vital signs in the Initial Vaccination Period and the Crossover Vaccination Period.
● To assess the immunogenicity of a 2-dose regimen of S-268019-b in the subset of immunogenicity subset.	● The following items for SARS-CoV-2 neutralizing antibody titer and anti-SARS-CoV-2 S-protein immunoglobulin G (IgG) antibody titers from Immunogenicity subset: - Geometric mean titer (GMT) - Geometric mean fold rise (GMFR) of antibody titer - Seroconversion rate
Exploratory	
● To assess the durability of vaccine efficacy in the Crossover Vaccination Period.	● The first occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 in the Crossover Vaccination Period. ● The first occurrence of asymptomatic SARS-CoV-2 infection in the Crossover Vaccination Period. Antibodies to SARS-CoV-2 N-protein were used to determine natural infection and to determine the incidence of asymptomatic infection acquired during study follow-up.
● To explore SARS-CoV-2 genetic variants in participants diagnosed with COVID-19.	● Nucleotide sequences of SARS-CoV-2 viral genomes detected in nasopharyngeal swabs from RT-PCR-positive participants analyzed with next-generation sequencing.

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Methodology:

This was a multicenter, randomized, observer-blind, placebo-controlled, cross-over phase 3 study to evaluate the efficacy, safety, and immunogenicity of S-268019-b in participants ≥ 18 years of age. Participants, investigators, and other site staff except persons in charge of management, dispensing and administration of the study interventions were blinded.

This study consisted of the Screening Period (day −28 to day 1), the Initial Vaccination Period (day 1 to day 224), and the Crossover Vaccination Period (day 225 to day 435).

In the Screening Period, potential participants who signed the informed consent form (ICF) were screened for study participation. On day 1 in the Initial Vaccination Period, eligible participants were randomly assigned to either the S-268019-b-preceding group or the placebo-preceding group in a 2:1 ratio. The target number of randomized participants was approximately 54,915 (36,610 participants in the S-268019-b-preceding group, 18,305 participants in the placebo-preceding group). The randomization was stratified by age group (18 to 64 years of age and ≥ 65 years of age). Participants assigned to the S-268019-b-preceding group received S-268019-b on day 1 and day 29, and participants assigned to the placebo-preceding group received placebo on the same schedule. The Initial Vaccination Period went on for 6 months after the second vaccination. Participants who completed the Initial Vaccination Period proceeded to the Crossover Vaccination Period starting on day 225. In the Crossover Vaccination Period, participants assigned to the S-268019-b-preceding group received placebo on day 225 and day 253 and participants assigned to the placebo-preceding group received S-268019-b on the same schedule. The Crossover Vaccination Period went on after the fourth vaccination to monitor for COVID-19-related symptoms and to monitor for safety. Participants were assessed for the efficacy, safety, and immunogenicity in accordance with the planned schedule of activities (SoA). Surveillance for COVID-19-related symptoms during the study was performed using participant diary. When a participant reported any COVID-19-related symptoms, or a participant reported symptoms that met the criteria for COVID-19, the investigator or designee instructed the participant to visit the site as soon as possible but no later than 3 days from that day to collect a nasopharyngeal swab sample for RT-PCR test. The RT-PCR-positive participants were further monitored until they recovered from COVID-19. The COVID-19 Follow-up Visit was scheduled 28 days after the Potential COVID-19 Illness Visit. If any COVID-19-related symptom persisted at the time of the COVID-19 Follow-up

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Visit, the investigator was to continue the follow-up until the participant had fully recovered or been medically stable.

Number of Participants (Planned and Analyzed):

Planned: Approximately 54,915 participants (36,610 in the S-268019-b-preceding group, 18,305 in the placebo-preceding group)

Randomized: 9,902 (6,600 in the S-268019-b-preceding group, 3,302 in the placebo-preceding group)
At the primary analysis, 8,594 (5,727 in the S-268019-b-preceding group, 2,867 in the placebo-preceding group), as of 31 Mar 2022 (data cutoff date)

Analyzed for efficacy:

- Full analysis set (FAS):

  8,562 (5,710 in the S-268019-b-preceding group, 2,852 in the placebo-preceding group), as of 31 Mar 2022 (data cutoff date)

  9,866 (6,581 in the S-268019-b-preceding group, 3,285 in the placebo-preceding group) for final analysis
- Modified intent-to-treat (mITT) population:

  7,889 (5,256 in the S-268019-b-preceding group, 2,633 in the placebo-preceding group), as of 31 Mar 2022 (data cutoff date)

  8,401 (5,596 in the S-268019-b-preceding group, 2,805 in the placebo-preceding group) for final analysis
- Per protocol set (PPS):

  7,817 (5,212 in the S-268019-b-preceding group, 2,605 in the placebo-preceding group), as of 31 Mar 2022 (data cutoff date)

  8,204 (5,470 in the S-268019-b-preceding group, 2,734 in the placebo-preceding group) for final analysis
- Crossover subset:

  6,421 (4,324 in the S-268019-b-preceding group, 2,097 in the placebo-preceding group) for final analysis

Analyzed for immunogenicity:

- Immunogenicity subset: 98 (64 in the S-268019-b-preceding group, 34 in the placebo-preceding group)

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Analyzed for safety:

- Safety analysis set (SAS): 9,866 (6,581 in the S-268019-b-preceding group, 3,285 in the placebo-preceding group)

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria
   - Male or female participants who were ≥ 18 years of age, at the time of signing the informed consent form.
   - Agreed not to participate in any other SARS-CoV-2 prevention trial during the study follow-up.
   - Capable of using Diary without difficulties (if applicable, with assistance by caregiver).
2. Exclusion criteria
   - Current or history of a laboratory-confirmed diagnosis of SARS-CoV-2 infection or COVID-19.
   - Unstable current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disease that, in the opinion of the investigator or subinvestigator, would constitute a safety concern or confound data interpretation.
   - Immunosuppression (immunodeficiency, acquired immunodeficiency syndrome [AIDS], use of systemic steroids, use of immunosuppressants within the past 6 months prior to the first dose of study intervention, treatment for malignant tumors, other immunosuppressive therapy).
   - Individuals considered to have hypersensitivity to any of the study interventions or components thereof, or drug or other allergy that, in the opinion of the investigator or subinvestigator, contraindicates participation in the study (except for pollinosis and atopic dermatitis).
   - Participant had a contraindication to intramuscular (IM) injections or blood draws.
   - Previous vaccination against SARS-CoV-2.
   - Any inactivated vaccine received within 14 days prior to the first dose of study intervention.
   - Any live vaccine received within 28 days prior to the first dose of study intervention.

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- Immunoglobulin preparations, blood products, or a blood transfusion within 3 months prior to the first dose of study intervention.
- Current enrollment or past participation within the last 30 days before signing of the ICF for this study in any other clinical study involving an investigational study intervention or any other type of medical research.
- Exposure to 4 or more new chemical entities within 12 months prior to the first dose of study intervention.
- Ineligibility for the study as considered by the investigator or subinvestigator.
- An immediate family member or household member of this study's personnel (both the sponsor and site personnel).

Test Product, Dose and Mode of Administration, Lot Number:

1. Test Product (S-268019-b)
   - S-268019 solution for intramuscular injection (containing S-910823) 40 µg/mL (antigen)
   - S-268019 oil-in-water emulsion (adjuvant)

2. Dose and Mode of Administration

S-268019 solution for IM injection (containing S-910823) 40 µg/mL and S-268019 oil-in-water emulsion adjuvant were mixed at a ratio of 1:1 (each 0.25 mL for one dose), and 0.5 mL of the mixture was administered at a 4-week interval for a total of two doses respectively in the Initial Vaccination Period and the Crossover Vaccination Period.

3. Packaging Lot Number

S-268019 antigen: [redacted]

S-268019 adjuvant: [redacted]

Duration of Treatment:
Two doses separated by 28 days each for 2 periods.

Reference Therapy, Dose and Mode of Administration, Lot Number:
Not applicable.

Criteria for Evaluation:

Efficacy Assessment:
In this study, the vaccine breakthrough cases were investigated as an efficacy assessment.
A patient was defined to have symptomatic COVID-19 when the patient had at least one of the following COVID-19-related symptoms and his or her RT-PCR test result was positive. The medical monitor of the sponsor confirmed whether each potentially symptomatic patient had symptomatic COVID-19 or not.

COVID-19-related symptoms	
Duration	**Symptom**
No minimum duration	Fever (Oral ≥ 38.0°C [≥ 100.4°F] or Axillary ≥ 37.5 °C [≥ 99.5°F]), Shortness of breath, Difficulty breathing
Must be present for ≥ 2 days	Chills, Cough, Fatigue, Muscle aches, Body aches, Headache, New loss of taste, New loss of smell, Sore throat, Congestion, Runny nose, Nausea, Vomiting, Diarrhea

If a participant was confirmed to have symptomatic COVID-19, the investigator evaluated if the maximum intensity during the course of the disease met the criteria for severe COVID-19. Severe COVID-19 was defined as 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, oxygen saturation ≤ 93% on room air at sea level, or partial pressure of oxygen to fraction of inspired oxygen ratio [PaO_2/FiO_2 ratio] < 300 mmHg)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation [ECMO])
- Evidence of shock (systolic blood pressure [SBP] < 90 mmHg, diastolic blood pressure [DBP] < 60 mmHg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an intensive care unit (ICU)
- Death

Asymptomatic SARS-CoV-2 infection was defined as a case in which a participant had positive result of anti-SARS-CoV-2 N-protein antibody test and did not meet the criteria of symptomatic COVID-19.

Immunogenicity Assessment:
Anti-SARS-CoV-2 S-protein IgG antibodies, anti-SARS-CoV-2 N-protein antibodies, and SARS-CoV-2 neutralizing antibodies.

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Safety Assessment:

A treatment-emergent adverse event (TEAE) was defined as an AE occurring after the initial administration of the study intervention.

The term "reactogenicity" refers to the property of a vaccine of being able to produce common solicited adverse reactions, especially excessive immunological responses and associated signs and symptoms. In order to assess the reactogenicity of S-268019-b, predefined solicited local and systemic AEs occurring after the first and second vaccinations and until 7 days post-vaccination in the Initial Vaccination Period were collected using e-Diary or paper diaries.

Solicited Local Adverse Events	Solicited Systemic Adverse Events
Pain	Fever (Oral ≥38.0 °C [≥100.4°F] or Axillary ≥37.5 °C [≥99.5°F])
Erythema/Redness	Nausea/Vomiting
Induration	Diarrhea
Swelling	Headache
	Fatigue
	Myalgia

A MAAE was defined as an AE leading to medically-attended visits that were not routine study visits, for example, hospital, emergency room (ER), urgent care clinic, or other visits to or from medical personnel for an AE. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled illness visits were not considered MAAEs.

Potential immune-mediated diseases were collected as AESIs of S-268019-b.

AEs were collected from the date of signing of the ICF to 4 weeks after the second vaccination (Initial Vaccination Period), and from the third vaccination to 4 weeks after the fourth vaccination (Crossover Vaccination Period). All SAEs, MAAEs and AESIs were collected from the date of signing of the ICF until end of the study.

Physical examination results and vital signs were also assessed in this study.

The investigator or subinvestigator assessed the intensity of solicited AEs reported during the study by referring to the Food and Drug Administration (FDA) guidance. The intensity of each non-solicited AE and SAE was assessed and classified into grade 1 to 5 defined in the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

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Statistical Methods:

Efficacy Analyses:

The primary endpoint was analyzed on the mITT population and supported by analysis of the PPS.

As the primary efficacy analysis, the plan was to use a Poisson regression model with robust variance to analyze the primary endpoint, which included age as a baseline covariate as well as the log of the follow-up time as an offset. The vaccine efficacy was estimated from the model, which gave the relative risk in the incidence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 occurring during approximate six months (ie, from 14 days post second vaccination in the Initial Vaccination Period to the end of the Initial Vaccination Period). The vaccine efficacy was calculated as 1 minus the relative risk of the primary endpoint among the S-268019-b-preceding group (S-268019-b) versus the placebo-preceding group (placebo). The interim analysis was planned when approximately 50% (33 cases) and 75% (50 cases) of the total amount of statistical information was available. Since the incidence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 had reached the predefined target number (66 participants) until the end of Mar 2022, the primary analysis was conducted using the 31 Mar 2022 cutoff data which were database locked and unblinded on 21 Jul 2022. No interim analyses under the blinded condition were conducted. If the Poisson regression model with robust variance fails to converge, an alternative approach was to be implemented. The efficacy was to be demonstrated if the null hypothesis vaccine efficacy ≤ 30% is rejected, that is, when the lower limit of 95% confidence interval (CI) for vaccine efficacy is > 30%.

In addition, 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.

Supplemental analysis using the same method as the primary efficacy analysis on the mITT population was conducted in the PPS.

The (key) secondary efficacy endpoints were analyzed using the same manner as the primary efficacy analysis.

Immunogenicity Analyses:

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The secondary immunogenicity endpoints were analyzed using the Immunogenicity subset. For the serum levels for SARS-CoV-2 neutralizing antibody and anti-spike protein IgG antibody, the GMT at each study visit, and the GMFR of antibody titer comparing to the baseline at each post-vaccination study visit, along with 95% CI were summarized by 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. For SARS-CoV-2 neutralizing antibody and anti-spike protein IgG antibody seroconversion at each post-vaccination study visit, seroconversion rate, along with 95% CI were estimated for each intervention group. The 95% CI was calculated using the Clopper-Pearson method. Seroconversion rate was defined as the percentage of participants with a ≥ 4-fold increase in post-vaccination antibody titer from baseline.

Safety Analyses:

All safety analyses were performed using the SAS.

Reactogenicity was measured with solicited local AEs (pain, erythema/redness, induration and swelling) and systemic AEs (fever, nausea/vomiting, diarrhea, headache, fatigue and myalgia) collected in the electronic case report form (eCRF). The number and percentage of participants who had solicited local AEs and systemic AEs within 7 days after the first and second vaccinations in the Initial Vaccination Period were summarized by intervention group. These events were tabulated by type of reactions, severity grade, time to onset, and duration.
Adverse events were classified by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.1 developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

A TEAE was defined as an AE occurring after the first dose of study intervention. Of the AE reported in the eCRF, TEAE was used for the safety analysis.

The number and percentage of participants with TEAEs were summarized by intervention group.

The number of participants with at least one TEAE leading to death, other serious TEAEs, MAAEs, AESIs, and discontinuation of study intervention were similarly summarized. Treatment-related AEs were summarized in the same manner as TEAEs.

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Treatment-related AEs were defined as AEs considered as "related" to the study intervention.

A summary of TEAEs by MedDRA SOC and PT was provided by intervention group, showing the number and percentage of participants with AEs. In addition, data was summarized by severity, time to onset, and duration. Treatment-related AEs were summarized in the same manner.

All AEs, including those occurring prior to the first dose of study intervention, were listed.

Summary statistics for vital signs and change from baseline at each scheduled time point were presented by intervention group.

Summary of Results:

The primary analysis with unblinding was conducted using the 31 Mar 2022 cutoff data. In this report, the primary efficacy endpoint and the key secondary efficacy endpoints using the 31 Mar 2022 cutoff data, and the final analysis using the final data were included.

Study population:

A total of 12,976 participants were enrolled in Vietnam. Of them, 3,074 participants were not randomized because entry criteria were not met. A total of 9,902 participants were randomized to one of the two treatment groups: 6,600 in the S-268019-b-preceding group and 3,302 in the placebo-preceding group. Of the 9,902 randomized participants, 8,401 were included in the mITT population (5,596 and 2,805 participants in the S-268019-b-preceding group and the placebo-preceding group, respectively). At the primary analysis using the 31 Mar 2022 cutoff data, of the 8,594 randomized participants, 7,889 were included in the mITT population (5,256 and 2,633 participants in the S-268019-b-preceding group and the placebo-preceding group, respectively).

There were no substantial differences in the demographic or baseline characteristics of participants in the mITT population between the treatment groups. With final data, the proportion of the male participants was 68.4% in the S-268019-b-preceding group and 66.0% in the placebo-preceding group. The median age (min-max) of the participants was 38.0 (17-98) years in the S-268019-b-preceding group and 38.0 (18-91) years in the placebo-preceding group. The mean BMI (SD) was 22.101 (2.990) in the S-268019-b-preceding group and 22.148 (3.261) in the placebo-preceding group.

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Efficacy:

Analysis of the primary efficacy of the first occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 in the Initial Vaccination Period with onset at least 14 days following the second vaccination in the mITT population showed that the incidence rate per 1,000 person-years (95% CI) was 776.41 (682.04 to 880.19) in the S-268019-b-preceding group and 1272.87 (1101.32 to 1463.57) in the placebo-preceding group at the 31 Mar 2022 data cutoff. The vaccine efficacy versus placebo (95% CI) was 39.1% (26.6 to 49.5), but the vaccine efficacy > 30% was not statistically demonstrated (one-sided P = 0.0723). The final analysis showed that the incidence rate per 1,000 person-years (95% CI) was 142.12 (127.04 to 158.49) in the S-268019-b-preceding group and 215.82 (189.32 to 244.99) in the placebo-preceding group. The vaccine efficacy versus placebo (95% CI) was 34.2% (21.9 to 44.6), but the vaccine efficacy > 30% was not statistically demonstrated (one-sided P = 0.2409).

Analysis of the key secondary efficacy of the first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 in the Initial Vaccination Period with onset at least 14 days following the second vaccination in the mITT population showed that the incidence rate per 1,000 person-years (95% CI) was 0.00 (0.00 to 11.31) in the S-268019-b-preceding group and 6.06 (0.15 to 33.75) in the placebo-preceding group at the 31 Mar 2022 data cutoff. The vaccine efficacy versus placebo (95% CI) was 100.0% (CI not calculated). The final analysis showed that the incidence rate per 1,000 person-years (95% CI) was 0.00 (0.00 to 1.56) in the S-268019-b-preceding group and 0.86 (0.02 to 4.77) in the placebo-preceding group. The vaccine efficacy versus placebo (95% CI) was 100.0% (CI not calculated).

Analysis of the key secondary efficacy of the first occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 in the Initial Vaccination Period in the mITT population showed that the incidence rate per 1,000 person-years (95% CI) was 422.01 (379.77 to 467.67) in the S-268019-b-preceding group and 608.34 (536.90 to 686.63) in the placebo-preceding group at the 31 Mar 2022 data cutoff. The vaccine efficacy versus placebo (95% CI) was 30.6% (19.0 to 40.6). The final analysis showed that the incidence rate per 1,000 person-years (95% CI) was 155.72 (141.77 to 170.67) in the S-268019-b-preceding group and 217.45 (194.02 to 242.92) in the placebo-preceding group. The vaccine efficacy versus placebo (95% CI) was 28.4% (17.1 to 38.2).

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Analysis of the key secondary efficacy of the first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 in the Initial Vaccination Period in the mITT population showed that the incidence rate per 1,000 person-years (95% CI) was 0.00 (0.00 to 4.19) in the S-268019-b-preceding group and 2.25 (0.06 to 12.55) in the placebo-preceding group at the 31 Mar 2022 data cutoff. The vaccine efficacy versus placebo (95% CI) was 100.0% (CI not calculated). The final analysis showed that the incidence rate per 1,000 person-years (95% CI) was 0.00 (0.00 to 1.22) in the S-268019-b-preceding group and 0.66 (0.02 to 3.70) in the placebo-preceding group. The vaccine efficacy versus placebo (95% CI) was 100.0% (CI not calculated).

Analysis of the secondary efficacy of the first occurrence of asymptomatic SARS-CoV-2 infection in the Initial Vaccination Period beginning 14 days following the second vaccination in the mITT population for the final analysis showed that the incidence rate per 1,000 person-years (95% CI) was 1753.45 (1685.96 to 1822.95) in the S-268019-b-preceding group and 2034.96 (1927.64 to 2146.69) in the placebo-preceding group. The vaccine efficacy versus placebo (95% CI) was 13.9% (7.2 to 20.1).

Subgroup analysis of the first occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 in the Initial Vaccination Period with the onset at least 14 days following the second vaccination by age (18 to 64 years of age, ≥ 65 years of age) in the mITT population for the final analysis showed that the vaccine efficacy versus placebo (95% CI) was higher in the 18 to 64 years of age subgroup compared to the ≥ 65 years of age subgroup (35.1% [22.6 to 45.6] and 12.4% [−91.5 to 59.9], respectively).

The post hoc analysis of the first occurrence of symptomatic COVID-19 with hospitalization with symptom onset at least 14 days following the second vaccination in the Initial Vaccination Period in the mITT population showed that the incidence rate per 1,000 person-years (95% CI) was 3.07 (0.08 to 17.09) in the S-268019-b-preceding group and 18.18 (3.75 to 53.14) in the placebo-preceding group at the 31 Mar 2022 data cutoff. The vaccine efficacy versus placebo (95% CI) was 83.2% (−61.5 to 98.2). The final analysis showed that the incidence rate per 1,000 person-years (95% CI) was 1.27 (0.26 to 3.71) in the S-268019-b-preceding group and 3.43 (0.93 to 8.77) in the placebo-preceding group. The vaccine efficacy versus placebo (95% CI) was 62.7% (−67.0 to 91.6).

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A total of 249 genome data of SARS-CoV-2 were obtained in this study (186 [107 in the S-268019-b-preceding group and 79 in the placebo-preceding group] in the Initial Vaccination Period and 63 [42 in the S-268019-b-preceding group and 21 in the placebo-preceding group] in the Crossover Vaccination Period).

In the Initial Vaccination Period, Omicron variants were determined for 83 participants in the S-268019-b-preceding group and for 65 participants in the placebo-preceding group based on genome sequence. Delta variants were determined for 4 participants in the S-268019-b-preceding group and for 4 participants in the placebo-preceding group based on genome sequence.

In the Crossover Vaccination Period, Omicron variants were determined for 39 participants in the S-268019-b-preceding group and for 19 participants in the placebo-preceding group based on genome sequence. No Delta variants were determined in either treatment group based on genome sequence.

Immunogenicity:
The GMTs of SARS-CoV-2 neutralizing antibody clearly increased in the S-268019-b-preceding group after the study vaccination, while nearly unchanged until it increased after vaccination of S-268019-b in the placebo-preceding group; the GMTs (95% CI) on baseline, day 29, day 57, day 97, day 225 and day 435 were 2.50 (CI not calculated), 2.58 (2.49 to 2.68), 34.66 (27.04 to 44.41), 22.97 (13.81 to 38.23), 6.21 (3.84 to 10.04) and 18.88 (6.93 to 51.41) in the S-268019-b-preceding group, and 2.50 (CI not calculated), 2.50 (CI not calculated), 2.69 (2.31 to 3.14), 2.66 (2.31 to 3.06), 2.50 (CI not calculated) and 16.82 (6.73 to 42.04) in the placebo-preceding group, respectively.

For the purpose of standardization of neutralizing activity of anti-SARS-CoV-2 antibodies among different vaccines, the neutralizing antibody titers were converted to the international standard units (IU/mL) of the WHO International Standards for anti-SARS-CoV-2 immunoglobulin. The GMT on day 57 was 344 IU/mL in the S-268019-b-preceding group.

The geometric mean titer ratios (GMTRs) (95% CI) of SARS-CoV-2 neutralizing antibody (S-268019-b/placebo) obtained by using analysis of covariance (ANCOVA) model were 1.03 (0.98 to 1.09) on day 29, 12.65 (8.71 to 18.37) on day 57, 8.84 (4.33

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to 18.06) on day 97, 2.64 (1.48 to 4.70) on day 225 and 1.31 (0.32 to 5.36) on day 435.

The GMFRs (95% CI) of SARS-CoV-2 neutralizing antibody were 1.03 (1.00 to 1.07) in the S-268019-b-preceding group and 1.00 (CI not calculated) in the placebo-preceding group on day 29, 13.86 (10.82 to 17.76) and 1.08 (0.92 to 1.25) on day 57, 9.19 (5.52 to 15.29) and 1.07 (0.93 to 1.23) on day 97, 2.48 (1.54 to 4.02) and 1.00 (CI not calculated) on day 225 and 7.55 (2.77 to 20.56) and 6.73 (2.69 to 16.82) on day 435.

The proportions of SARS-CoV-2 neutralizing antibody seroconversion (95% CI) were 0.0% (0.0 to 5.7) in the S-268019-b-preceding group and 0.0% (0.0 to 10.9) in the placebo-preceding group on day 29, 93.1% (83.3 to 98.1) and 3.6% (0.1 to 18.3) on day 57, 80.0% (59.3 to 93.2) and 0.0% (0.0 to 28.5) on day 97, 31.3% (11.0 to 58.7) and 0.0% (0.0 to 30.8) on day 225, 66.7% (34.9 to 90.1) and 75.0% (34.9 to 96.8) on day 435. The differences between the two groups (95% CI) were 0.0% (CI not calculated) on day 29, 89.5% (80.1 to 99.0) on day 57, 80.0% (64.3 to 95.7) on day 97, 31.3% (8.5 to 54.0) on day 225 and −8.3% (−48.5 to 31.8) on day 435.

The GMTs of anti-spike protein IgG antibody clearly increased in the S-268019-b-preceding group after the study vaccination, while nearly unchanged until it increased after vaccination of S-268019-b in the placebo-preceding group; the GMTs (95% CI) on baseline, day 29, day 57, day 97, day 225 and day 435 were 3.72 (3.43 to 4.04), 580.12 (454.11 to 741.08), 25209.25 (17163.57 to 37026.44), 11287.45 (7272.11 to 17519.89), 1316.53 (740.82 to 2339.63) and 3680.49 (1078.79 to 12556.63) in the S-268019-b-preceding group, and 4.27 (3.50 to 5.21), 4.02 (3.29 to 4.90), 6.39 (3.10 to 13.19), 10.25 (3.17 to 33.15), 14.07 (5.16 to 38.38) and 2820.92 (904.66 to 8796.29) in the placebo-preceding group.

The GMTRs (95% CI) of anti-spike protein IgG antibody (S-268019-b/placebo) obtained by using ANCOVA model were 139.47 (96.53 to 201.51) on day 29, 3774.13 (1803.04 to 7900.01) on day 57, 1137.92 (474.54 to 2728.64) on day 97, 105.97 (41.06 to 273.55) on day 225 and 1.65 (0.30 to 9.10) on day 435.

The GMFRs (95% CI) of anti-spike protein IgG antibody were 156.88 (122.16 to 201.47) in the S-268019-b-preceding group and 0.93 (0.82 to 1.05) in the placebo-preceding group on day 29, 6710.95 (4556.29 to 9884.54) and 1.46 (0.75 to 2.85) on day 57, 3229.06 (2079.40 to 5014.34) and 2.32 (0.88 to 6.13) on day 97, 387.22

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(217.89 to 688.13) and 3.10 (1.29 to 7.46) on day 225, and 1082.50 (317.29 to 3693.13) and 578.16 (169.08 to 1977.04) on day 435.

The proportions of anti-spike protein IgG antibody seroconversion (95% CI) were 100.0% (94.2 to 100.0) in the S-268019-b-preceding group and 0.0% (0.0 to 10.9) in the placebo-preceding group on day 29, 98.2% (90.6 to 100.0) and 7.1% (0.9 to 23.5) on day 57, 100.0% (86.3 to 100.0) and 36.4% (10.9 to 69.2) on day 97, 100.0% (79.4 to 100.0) and 50.0% (18.7 to 81.3) on day 225 and 100.0% (73.5 to 100.0) and 100.0% (63.1 to 100.0) on day 435. The differences between the two groups (95% CI) were 100.0% (CI not calculated) on day 29, 91.1% (81.0 to 100.0) on day 57, 63.6% (35.2 to 92.1) on day 97, 50.0% (19.0 to 81.0) on day 225 and 0.0% (CI not calculated) on day 435.

Safety:
In the safety analyses except for vital signs, the treatment groups represent the study intervention administered in the Initial Vaccination Period or in the Crossover Vaccination Period. For clarification, the treatment groups in the Crossover Vaccination Period are stated as the S-268019-b group (Crossover) and the placebo group (Crossover).

In the Initial Vaccination Period, 12,000 AEs were reported in 54.0% (3,555 of 6,581 participants) in the S-268019-b group and 3,612 AEs were reported in 41.3% (1,356 of 3,285 participants) in the placebo group. And 10,004 treatment-related AEs were reported in 46.1% (3,035 of 6,581 participants) in the S-268019-b group and 2,524 treatment-related AEs were reported in 30.4% (998 of 3,285 participants) in the placebo group.

In the Crossover Vaccination Period, 162 AEs were reported in 5.0% (125 of 2,502 participants) in the S-268019-b group (Crossover) and 341 AEs were reported in 4.6% (237 of 5,150 participants) in the placebo group (Crossover). Nine treatment-related AEs were reported in 0.3% (7 of 2,502 participants) in the S-268019-b group (Crossover) and 29 treatment-related AEs were reported in 0.5% (24 of 5,150 participants) in the placebo group (Crossover).

In the Initial Vaccination Period, 6,016 solicited systemic AEs were reported in 32.7% (2,149 of 6,581 participants) in the S-268019-b group and 1,941 solicited systemic AEs were reported in 23.4% (770 of 3,285 participants) in the placebo group.

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In the Initial Vaccination Period, 4,034 solicited local AEs were reported in 37.7% (2,480 of 6,581 participants) in the S-268019-b group and 592 solicited local AEs were reported in 14.6% (479 of 3,285 participants) in the placebo group.

In the Initial Vaccination Period, 5,936 treatment-related solicited systemic AEs were reported in 32.4% (2,130 of 6,581 participants) in the S-268019-b group and 1,896 treatment-related solicited systemic AEs were reported in 23.0% (756 of 3,285 participants) in the placebo group.

In the Initial Vaccination Period, 3,966 treatment-related solicited local AEs were reported in 37.3% (2,454 of 6,581 participants) in the S-268019-b group and 579 treatment-related solicited local AEs were reported in 14.3% (470 of 3,285 participants) in the placebo group.

In the Initial Vaccination Period, AEs with a 5% or greater difference in incidence between the treatment groups were pain (25.6% in the S-268019-b group vs 8.6% in the placebo group, hereafter in the same order), fatigue (21.3% vs 14.1%), headache (18.7% vs 13.4%), myalgia (15.6% vs 7.8%) and injection site pain (14.0% vs 6.6%).

In the Crossover Vaccination Period, there were no AEs with a 5% or greater difference in incidence between the treatment groups.

None of the participants experienced grade 5 or grade 4 solicited systemic or local AEs after the first or second vaccinations in the Initial Vaccination Period, and most of the solicited systemic and local AEs were grade 1 or grade 2 in severity.
After the first vaccination in the Initial Vaccination Period, grade 3 solicited systemic AEs occurred in 26 participants (fever for 20 participants, fatigue for 3 participants, headache for 1 participant, fatigue and headache for 1 participant, fatigue and myalgia for 1 participant) in the S-268019-b group and 5 participants (fever for 4 participants and diarrhea for 1 participant) in the placebo group. Grade 3 solicited local AE occurred in 1 participant (pain) in the S-268019-b group. Among those grade 3 solicited systemic and local AEs, fever (20 participants in the S-268019-b group and 4 participants in the placebo group), fatigue (4 participants in the S-268019-b group), headache (2 participants in the S-268019-b group), myalgia (1 participant in the S-268019-b group), diarrhea (1 participants in the placebo group), and pain (1 participant in the S-268019-b group) were considered related to the study intervention.

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After the second vaccination in the Initial Vaccination Period, grade 3 solicited systemic AEs occurred in 54 participants (fever for 42 participants, fatigue for 7 participants, headache, diarrhea, myalgia for 1 participant each, fatigue and headache for 1 participant, fatigue, headache and nausea/vomiting for 1 participant) in the S-268019-b group and 11 participants (fever for 10 participants and myalgia for 1 participant) in the placebo group. Grade 3 solicited local AEs occurred in 3 participants (pain for 1 participant, and induration and swelling for 2 participants) in the S-268019-b group but did not occur in the placebo group. Among grade 3 solicited systemic AEs, all occurred in 54 participants in the S-268019-b group and those that occurred in 10 participants (fever for 9 participants and myalgia for 1 participant) in the placebo group were considered related to the study intervention. And all grade 3 solicited local AEs were considered related to the study intervention.

In the Initial Vaccination Period, 24 fatal SAEs (9 deaths, 2 craniocerebral injury, 1 each for completed suicide, septic shock, meningioma, hepatic cirrhosis, asthenia, road traffic accident, encephalitis, respiratory distress, acute coronary syndrome, multiple injuries, cardiac failure, respiratory failure, and chronic kidney disease) were reported in 0.4% (24 of 6,581 participants) in the S-268019-b group and 19 fatal SAEs (2 septic shock, 2 completed suicide, 1 for hepatic cirrhosis and multi-organ disorder, 1 each for pulmonary embolism, gastrointestinal stromal tumour, multiple injuries, death, haemorrhagic stroke, cirrhosis alcoholic, hepatic encephalopathy, diabetic nephropathy, pneumonia, cardiac failure, diabetes mellitus, cerebrovascular accident, and myocardial ischaemia) were reported in 0.5% (18 of 3,285 participants) in the placebo group. All fatal SAEs were considered unrelated to the study intervention. One fatal SAE (lung neoplasm) in the placebo group was not included in the safety analyses because it was not a TEAE as the onset was determined as prior to the administration of the study intervention.

In the Crossover Vaccination Period, 4 fatal SAEs (completed suicide, pneumonia, multi-organ disorder, and bronchitis) were reported in 0.2% (4 of 2,502 participants) in the S-268019-b group (Crossover) and 11 fatal SAEs (2 craniocerebral injury, 2 pneumonia, 2 death, 1 each for cerebrovascular accident, venom poisoning, hepatic cirrhosis, respiratory distress, and sudden death) were reported in 0.2% (11 of 5,150 participants) in the placebo group (Crossover). All fatal SAEs were considered unrelated to the study intervention.

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In the Initial Vaccination Period, 141 nonfatal SAEs were reported in 1.7% (115 of 6,581 participants) in the S-268019-b group and 95 nonfatal SAEs were reported in 2.3% (76 of 3,285 participants) in the placebo group. One SAE (grade 3 headache) in the S-268019-b group and 1 SAE (grade 2 hypersensitivity) in the placebo group were considered related to the study intervention. Both SAEs were "recovered/resolved".

In the Crossover Vaccination Period, 17 nonfatal SAEs were reported in 0.7% (17 of 2,502 participants) in the S-268019-b group (Crossover) and 42 nonfatal SAEs were reported in 0.7% (37 of 5,150 participants) in the placebo group (Crossover). All SAEs in the S-268019-b group (Crossover) and the placebo group (Crossover) were considered unrelated to the study intervention.

In the Initial Vaccination Period, 3 AESIs were reported in 0.0% (3 of 6,581 participants) in the S-268019-b group and 5 AESIs were reported in 0.2% (5 of 3,285 participants) in the placebo group. No treatment-related AESIs were reported either in the S-268019-b group or in the placebo group.

In the Crossover Vaccination Period, no AESIs were reported in the S-268019-b group (Crossover) and 2 AESIs were reported in 0.0% (2 of 5,150 participants) in the placebo group (Crossover). No treatment-related AESIs were reported either in the S-268019-b group (Crossover) or in the placebo group (Crossover).

In the Initial Vaccination Period, 343 MAAEs were reported in 2.6% (172 of 6,581 participants) in the S-268019-b group and 218 MAAEs were reported in 3.1% (101 of 3,285 participants) in the placebo group. A total of 6 treatment-related MAAEs were reported in 0.1% (6 of 6,581 participants) in the S-268019-b group and 1 treatment-related MAAE was reported in 0.0% (1 of 3,285 participants) in the placebo group. The treatment-related MAAEs were as follows: 2 grade 3 blood pressure increased, 1 each for grade 3 vaccination complication, grade 3 hypertensive urgency, grade 3 heart rate increased and grade 3 headache in the S-268019-b group and grade 2 hypersensitivity in the placebo group. All treatment-related MAAEs except for 1 grade 3 blood pressure increased and 1 grade 3 hypertensive urgency in the S-268019-b group were "recovered/resolved". Grade 3 blood pressure increased and grade 3 hypertensive urgency in the S-268019-b group were "not recovered/not resolved".

In the Crossover Vaccination Period, 40 MAAEs were reported in 0.9% (23 of 2,502 participants) in the S-268019-b group (Crossover) and 121 MAAEs were reported in

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1.2% (62 of 5,150 participants) in the placebo group (Crossover). No treatment-related MAAEs were reported in the S-268019-b group (Crossover) and 1 treatment-related MAAE was reported in 0.0% (1 of 5,150 participants) in the placebo group (Crossover). The treatment-related MAAE was grade 3 heart rate increased in the placebo group (Crossover) and the outcome was "recovered/resolved".

In the Initial Vaccination Period, 95 AEs leading to discontinuation of study intervention were reported in 1.2% (82 of 6,581 participants) in the S-268019-b group and 62 AEs leading to discontinuation of study intervention were reported in 1.5% (48 of 3,285 participants) in the placebo group. AEs leading to discontinuation of study intervention in ≥ 2 participants in the Initial Vaccination Period in the S-268019-b group were as follows: hypertension (16 participants), blood pressure increased (14 participants), death (9 participants), heart rate increased (5 participants), asthenia (4 participants), chronic fatigue syndrome and cardiac failure (3 participants each), pneumonia, anaemia, epilepsy, and hepatic enzyme increased (2 participants each). And AEs leading to discontinuation of study intervention in ≥ 2 participants in the Initial Vaccination Period in the placebo group were as follows: blood pressure increased (7 participants), hypertension (6 participants), COVID-19 (5 participants), asthenia (4 participants), hepatic enzyme increased and tachycardia (3 participants each). Among the AEs leading to discontinuation of study intervention in the Initial Vaccination Period, a case of grade 3 hypertensive urgency in the S-268019-b group was considered related to the study intervention and the outcome was "not recovered/not resolved".

In the Crossover Vaccination Period, 5 AEs leading to discontinuation of study intervention were reported in 0.2% (5 of 2,502 participants) in the S-268019-b group (Crossover) and 14 AEs leading to discontinuation of study intervention were reported in 0.3% (13 of 5,150 participants) in the placebo group (Crossover). An AE leading to discontinuation of study intervention in ≥ 2 participants in the Crossover Vaccination Period in the S-268019-b group (Crossover) was blood pressure increased (3 participants). AEs leading to discontinuation of study intervention in ≥ 2 participants in the Crossover Vaccination Period in the placebo group (Crossover) were blood pressure increased (4 participants) and hypertension (3 participants). None of the AEs leading to discontinuation of study intervention in the Crossover Vaccination Period were considered related to the study intervention in the S-268019-b group (Crossover) or in the placebo group (Crossover).

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The median duration of solicited systemic AEs after the first vaccination in the Initial Vaccination Period was 2.0 days in both treatment groups and the median duration of solicited local AEs after the first vaccination was 2.0 days in the S-268019-b group and 1.0 day in the placebo group. The median duration of treatment-related solicited systemic AEs after the first vaccination in the Initial Vaccination Period was 2.0 days in both treatment groups and the median duration of treatment-related solicited local AEs after the first vaccination in the Initial Vaccination Period was 2.0 days in the S-268019-b group and 1.0 day in the placebo group.

The median duration of solicited systemic AEs after the second vaccination in the Initial Vaccination Period was 2.0 days in both treatment groups and the median duration of solicited local AEs after the second vaccination in the Initial Vaccination Period was 2.0 days in the S-268019-b group and 1.0 day in the placebo group. The median duration of treatment-related solicited systemic AEs after the second vaccination in the Initial Vaccination Period was 2.0 days in both treatment groups and the median duration of treatment-related solicited local AEs after the second vaccination in the Initial Vaccination Period was 2.0 days in the S-268019-b group and 1.0 day in the placebo group.

The median timing of onset of solicited systemic AEs after the first vaccination in the Initial Vaccination Period was day 1.0 in the S-268019-b group and day 2.0 in the placebo group. The median timing of onset of solicited local AEs after the first vaccination in the Initial Vaccination Period was day 1.0 in both treatment groups. The median timing of onset of treatment-related solicited systemic AEs after the first vaccination in the Initial Vaccination Period was day 1.0 in the S-268019-b group and day 2.0 in the placebo-preceding group. The median timing of onset of treatment-related solicited local AEs after the first vaccination in the Initial Vaccination Period was day 1.0 in both treatment groups.

The median timing of onset of solicited systemic AEs after the second vaccination in the Initial Vaccination Period was day 1.0 in the S-268019-b group and day 2.0 in the placebo group. The median timing of onset of solicited local AEs after the second vaccination in the Initial Vaccination Period was day 1.0 in both treatment groups. The median timing of onset of treatment-related solicited systemic AEs after the second vaccination in the Initial Vaccination Period was day 1.0 in the S-268019-b group and day 2.0 in the placebo group. The median timing of onset of treatment-

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related solicited local AEs after the second vaccination in the Initial Vaccination Period was day 1.0 in both treatment groups.

The mean vital sign parameters (systolic/diastolic blood pressure, pulse rate, respiratory rate, and body temperature) in the S-268019-b-preceding group was similar to that in the placebo-preceding group at all time points after administration of S-268019-b.

CONCLUSIONS

The rate of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 whose onset was 14 days or later following the second vaccination was 776.41/1,000 person-years (95% CI: 682.04 to 880.19) in the S-268019-b-preceding group and 1272.87/1,000 person-years (95% CI: 1101.32 to 1463.57) in the placebo-preceding group at the 31 Mar 2022 data cutoff. The vaccine efficacy versus placebo (95% CI) was 39.1% (26.6 to 49.5). The lower limit of 95% CI was higher than 0, but did not exceed 30 which was the pre-defined efficacy threshold criteria. Therefore, we were unable to provide evidence that met the primary objective of showing the vaccine efficacy of 30% or higher against SARS-CoV-2 RT-PCR-positive symptomatic COVID-19.

The vaccine efficacy in terms of the incidences of SARS-CoV-2 RT-PCR-positive severe COVID-19 or that with hospitalization versus placebo was 100.0% (CI not calculated) or 62.7% (−67.0 to 91.6) in the final analysis, respectively. The demonstrated vaccine efficacy suggested the potential of S-268019-b for prevention of worsening or hospitalization.

In the immunogenicity evaluation, the GMTs of SARS-CoV-2 neutralizing antibody and anti-spike protein IgG antibody in the S-268019-b-preceding group clearly increased on day 57 and day 97 compared to baseline, while the antibodies were not increased in the placebo-preceding group. Considering that Omicron variants were predominant during the study period, the study results were consistent with the results of the approved vaccines against the original SARS-CoV-2. And S-268019-b was considered clinically acceptable in terms of safety as a recombinant protein subunit vaccine in adult participants.

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