2. SYNOPSIS

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Study Title:
A Phase 3, Randomized, Observer-Blind, Active-Controlled Study to Compare Immunogenicity against COVID-19 of S-268019 to the ChAdOx1 nCoV-19 vaccine

Investigators and Study Centers:
This study was a multicenter study conducted at 20 sites in Japan.

Publication (reference): Not applicable

Studied Period:
From 17 Jan 2022 (First participant informed consent) to 28 Mar 2023 (Last participant last observation)

Phase of Development: 3

Objectives:
Primary Vaccination Part

Objectives	Estimand/Endpoints
Primary	
• To assess the superiority of the immunogenicity of a 2-dose regimen of intramuscular injection of S-268019-b as compared to the ChAdOx1 nCoV-19 vaccine.	• Population: Immunogenicity Subset consisting of participants who had at least 1 valid immunogenicity result after the first administration of study intervention and had no evidence of past or present severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at baseline.
	• Endpoint: SARS-CoV-2 neutralizing antibody (NAb) titer measured 28 days after the second administration.
	• Intercurrent events: The data from the participants who withdrew from the study prior to having been observed to have SARS-CoV-2 NAb titer to be measured 28 days after the second administration were treated as missing.
	• Summary measure: geometric mean titer ratio (GMTR) is defined as the ratio of the geometric mean titer (GMT) of SARS-CoV-2 NAb for the S-268019-b group to that for the ChAdOx1

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	nCoV-19 group measured 28 days after the second administration.
Key Secondary	
• To assess the non-inferiority of the immunogenicity of a 2-dose regimen of intramuscular injection of S-268019-b as compared to the ChAdOx1 nCoV-19 vaccine.	• The seroconversion rate* of SARS-CoV-2 NAb titer 28 days after the second administration.
Secondary	
• To assess the efficacy of S-268019-b for the prevention of symptomatic infection of COVID-19 as compared to the ChAdOx1 nCoV-19 vaccine.	• The first occurrence of SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR)-positive COVID-19 with the onset at least 14 days after the second administration in participants seronegative and RT-PCR-negative at baseline. • The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 with the onset at least 14 days after the second administration in participants seronegative and RT-PCR-negative at baseline. • The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 in participants seronegative and RT-PCR-negative at baseline. • The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 in participants seronegative and RT-PCR-negative at baseline. • The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 with the onset at least 14 days after the second administration regardless of serostatus and RT-PCR status at baseline. • The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 with the onset at least 14 days after the second administration regardless of serostatus and RT-PCR status at baseline. • The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 regardless of serostatus and RT-PCR status at baseline.

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	• The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 regardless of serostatus and RT-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.	• The first occurrence of asymptomatic SARS-CoV-2 infection beginning at least 14 days after the second administration in participants seronegative and RT-PCR-negative at baseline. • The first occurrence of asymptomatic SARS-CoV-2 infection beginning at least 14 days after the second administration regardless of serostatus and RT-PCR status at baseline.
• 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 results of vital signs.
• To assess the immunogenicity of a 2-dose regimen of S-268019-b in the Immunogenicity Subset.	• The following items for SARS-CoV-2 NAb titer and anti-SARS-CoV-2 spike glycoprotein (S-protein)(S1/S2) immunoglobulin G (IgG) antibody titers from Immunogenicity Subset (excluding the primary and key secondary endpoints): – GMT – Geometric mean of fold rise (GMFR) – Seroconversion rate*
Exploratory	
• 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.
• To assess other immunological indices.	• Cellular immunity – Human leukocyte antigen (HLA)-A genotyping – Cytokine-producing cell count • Type 1 helper T cells/Type 2 helper T cells balance (Th1/Th2 balance)

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	– T cell cytokine assay • The NAb titer against variant of interest (VOI) and variant of concern (VOC)

* Seroconversion rate is defined as the percentage of participants with a ≥ 4-fold increase in postvaccination antibody titer from baseline.

Booster Vaccination Part

Objectives	Estimand/Endpoints
Primary	
• To verify non-inferiority of the immunogenicity 28 days after the booster vaccination with S-268019-b compared to the immunogenicity 28 days after the second administration of S-268019-b for primary vaccination.	• Population: Immunogenicity Subset for Booster Vaccination consists of participants who received primary vaccination with S-268019-b. The Immunogenicity Subset for Booster Vaccination consists of participants in the Immunogenicity Subset who had at least 1 valid immunogenicity result after the third administration of the study intervention (booster vaccination), and had no positive results in SARS-CoV-2 RT-PCR or anti-SARS-CoV-2 nucleocapsid protein (N-protein) antibody test before the booster vaccination.
	• Endpoint: SARS-CoV-2 NAb titer measured 28 days after the booster vaccination (Day 239).
	• Intercurrent events: The data from the participants who withdrew from the study prior to having been observed to have SARS-CoV-2 NAb titer on Day 239 were treated as missing.
	• Summary measure (co-primary endpoints): GMTR, estimated by the ratio of the GMT of the SARS-CoV-2 NAb titer on Day 239 to that on Day 57, the difference in the seroconversion rate* of the SARS-CoV-2 NAb titer on Day 57, and the seroresponse rate** of SARS-CoV-2 NAb titer on Day 239.
Secondary	
• To assess the efficacy of S-268019-b for the prevention of symptomatic infection of COVID-19 given as the booster vaccination.	• The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 with the onset at least 14 days after the booster vaccination in

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	participants seronegative and RT-PCR-negative before the booster vaccination. • The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 with the onset at least 14 days after the booster vaccination in participants seronegative and RT-PCR-negative before the booster vaccination. • The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 after the booster vaccination in participants seronegative and RT-PCR-negative before the booster vaccination. • The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 after the booster vaccination in participants seronegative and RT-PCR-negative before the booster vaccination. • The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 with the onset at least 14 days after the booster vaccination regardless of serostatus and RT-PCR status before the booster vaccination. • The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 with the onset at least 14 days after the booster vaccination regardless of serostatus and RT-PCR status before the booster vaccination. • The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 after the booster vaccination regardless of serostatus and RT-PCR status before the booster vaccination. • The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 after the booster vaccination regardless of serostatus and RT-PCR status before the booster vaccination.
• To assess the efficacy of S-268019-b for the prevention of asymptomatic infection of COVID-19 as the booster vaccination.	• The first occurrence of asymptomatic SARS-CoV-2 infection beginning at least 14 days after the booster vaccination in participants

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	seronegative and RT-PCR-negative before the booster vaccination. • The first occurrence of asymptomatic SARS-CoV-2 infection beginning at least 14 days after the booster vaccination regardless of serostatus and RT-PCR status before the booster vaccination.
• To assess the safety and reactogenicity of S-268019-b as the booster vaccination.	• The incidence of AEs, treatment-related AEs, SAEs, AESIs, MAAEs, solicited local AEs, and solicited systemic AEs, and results of vital signs.
• To assess the immunogenicity 28 days after the booster vaccination with S-268019-b to the immunogenicity 28 days after the second primary vaccination with the ChAdOx1 nCoV-19 vaccine.	• SARS-CoV-2 NAb titer measured 28 days after the booster vaccination (Day 239) – GMT – Seroresponse rate**
• To assess the immunogenicity of S-268019-b as the booster vaccination.	• The following items for SARS-CoV-2 NAb titer and anti-SARS-CoV-2 S-protein (S1/S2) IgG antibody titers (excluding the comparison with the primary vaccination part): – GMT – GMFR – Seroresponse rate**
Exploratory	
• To explore SARS-CoV-2 genetic variants in participants diagnosed with COVID-19 after the booster vaccination with S-268019-b.	• Nucleotide sequences of SARS-CoV-2 viral genomes detected in nasopharyngeal swabs from RT-PCR-positive participants analyzed with next-generation sequencing.
• To assess other immunological indices after the booster vaccination with S-268019-b.	• Cellular immunity – HLA-A genotyping – Cytokine-producing cell count • Th1/Th2 balance – T cell cytokine assay • The NAb titer against VOI and VOC

* Seroconversion rate was defined as the percentage of participants with a ≥ 4-fold increase in postvaccination antibody titer from baseline.

** Seroresponse rate was defined as the percentage of participants with a ≥ 4-fold increase in postvaccination antibody titer from the level before the booster vaccination.

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Methodology:
This was a multicenter, randomized, observer-blind, active-controlled study to evaluate the immunogenicity, efficacy, and safety of S-268019-b as primary vaccination compared to the ChAdOx1 nCoV-19 vaccine in participants ≥ 18 years of age. A total of 1000 eligible participants were to be randomized to either the S-268019-b group or the active control group in a 1:1 ratio on Day 1. Assignment was stratified by age (18 to 39 years, 40 to 64 years, and ≥ 65 years). Participants received two doses of the study vaccine separated by 28 days (on Day 1 and Day 29), as an intramuscular injection, and followed by approximately 12-month follow-up from the second administration.

This study consisted of a primary vaccination part and a booster vaccination part. Of the participants who had completed the second administration of primary vaccination, only those who agreed to receive the third vaccination for booster were given a booster vaccination with S-268019-b, and the participants proceeded to the booster vaccination part. The booster vaccination was given after completion of the evaluation on Day 211, and after the booster vaccination, the study continued as an open-label study. In the booster vaccination part, non-inferiority of the immunogenicity of S-268019-b given as the booster vaccination compared to the immunogenicity of S-268019-b given as the primary vaccination was verified, and the immunogenicity, safety, and efficacy for the prevention of infection of S-268019-b administered for booster vaccination were evaluated.

Number of Participants (Planned and Analyzed):

Primary Vaccination Part
Planned: 1000

Randomized: 1225 (613 in the S-268019-b group, 612 in the active control group)

Analyzed for immunogenicity:

- Immunogenicity Subset: 1144 (563 in the S-268019-b group, 581 in the active control group)
- Immunogenicity Evaluable Subset: 1069 (515 in the S-268019-b group, 554 in the active control group)

Analyzed for efficacy:

- Full Analysis Set (FAS): 1220 (610 in the S-268019-b group, 610 in the active control group)

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- Modified intent-to-treat (mITT) population: 1161 (573 in the S-268019-b group, 588 in the active control group)

Analyzed for safety:
Safety Analysis Set: 1221 (611 in the S-268019-b group, 610 in the active control group)

Booster Vaccination Part
Analyzed for immunogenicity:

- Immunogenicity Subset for Booster Vaccination: 592 (278 from the S-268019-b group, 314 from the active control group)
- Immunogenicity Evaluable Subset for Booster Vaccination: 561 (262 from the S-268019-b group, 299 from the active control group)

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria

- Male and female ≥ 18 years of age at the time of signing the informed consent form (ICF).
- Agree not to participate in any other SARS-CoV-2 prevention trial during the study follow-up.
- Capable of using the e-Diary without difficulties.

2. Exclusion criteria

- Current or history of a laboratory-confirmed diagnosis of SARS-CoV-2 infection or COVID-19.
- Immunosuppression (immunodeficiency, acquired immunodeficiency syndrome [AIDS], use of systemic steroids, use of immunosuppressants within the past 6 months prior to the first administration of study intervention, treatment for malignant tumors, other immunosuppressive therapy).
- Recurrent severe infections within the past 6 months.
- History of central or peripheral demyelinating disease, or idiopathic thrombocytopenic purpura.
- Clinically significant bleeding disorder, or prior history of significant bleeding or bruising following intramuscular injections or venipuncture.

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- Previous episodes of capillary leak syndrome.
- Previous vaccination against SARS-CoV-2.
- Any inactivated vaccine or live vaccine received within 14 days or 28 days. respectively, prior to the first administration of study intervention.
- Immunoglobulin preparations, blood products, or a blood transfusion within 3 months prior to the first administration of study intervention.

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

1. Test Product
   - S-268019 injectable (containing S-910823) 40 μg/mL (antigen)
   - S-268019 oil in water emulsion for injection 1 mL (adjuvant)
   - S-268019 oil in water emulsion for injection 0.9 mL (adjuvant)
2. Dose and Mode of Administration

   S-268019 injectable (containing S-910823) 40 μg/mL (antigen) 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 twice at a 4-week interval.
3. Packaging Lot Number
   - S-268019 solution for intramuscular injection (containing S-910823) 40 μg/mL: [redacted]
   - S-268019 oil-in-water emulsion adjuvant for injection 1 mL: [redacted]
   - S-268019 oil-in-water emulsion adjuvant for injection 0.9 mL: [redacted]

Duration of Treatment:

Primary Vaccination Part

Two doses (single dose of study intervention was injected intramuscularly twice at a 28-day interval)

Booster Vaccination Part

Single dose

Reference Therapy, Dose, and Mode of Administration, Lot Number:

1. Reference Therapy

   ChAdOx1 nCoV-19 vaccine (Vaxzevria Intramuscular Injection, AstraZeneca)

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2. Dose and Mode of Administration
   A dose of 0.5 mL was administered twice at a 4-week interval.
3. Packaging Lot Number
   [redacted]

Criteria for Evaluation:

Immunogenicity Assessments

Blood samples for immunogenicity assessments were collected at the prespecified timepoints. Anti-SARS-CoV-2 N-protein antibodies, anti-SARS-CoV-2 S-protein (S1/S2) IgG antibodies, and NAb titers were analyzed to evaluate the immunogenicity of S-268019-b compared to the active control vaccine.

Primary Vaccination Part

The primary immunogenicity endpoint was the GMT of SARS-CoV-2 NAb of 28 days after the second administration.

The key secondary immunogenicity endpoint was the seroconversion rate for SARS-CoV-2 NAb titer 28 days after the second administration. The seroconversion rate was defined as the percentage of participants with a ≥ 4-fold increase in postvaccination antibody titer from baseline.

The secondary immunogenicity endpoints were GMT, GMFR, and seroconversion rates of SARS-CoV-2 NAb and anti-SARS-CoV-2 S-protein (S1/S2) IgG antibody at each visit.

Booster Vaccination Part

The primary immunogenicity endpoints were the GMT and seroresponse rate of SARS-CoV-2 NAb 28 days after the booster vaccination (Day 239). The seroresponse rate was defined as the percentage of participants with a ≥ 4-fold increase in postvaccination antibody titer from the level before the booster vaccination.

The secondary immunogenicity endpoints were GMT, GMFR, and seroresponse rates for SARS-CoV-2 NAb and anti-SARS-CoV-2 S-protein (S1/S2) IgG antibody at each visit.

Efficacy Assessment:

Surveillance of COVID-19-related symptoms was performed throughout the study. Suspected COVID-19 participants were to visit a study site to undergo the SARS-CoV-2 RT-PCR test. Participants who were positive for the RT-PCR test and met the criteria for symptomatic COVID-19 were identified, and the severity of

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symptomatic COVID-19 (severe or non-severe) was evaluated for efficacy assessments. Anti-SARS-CoV-2 N-protein antibodies were used to determine the asymptomatic SARS-CoV-2 infection.

Primary Vaccination Part
The efficacy endpoints were as follows:

- The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 with the onset at least 14 days after the second administration in participants seronegative and RT-PCR-negative at baseline.
- The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 with the onset at least 14 days after the second administration in participants seronegative and RT-PCR-negative at baseline.
- The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 in participants seronegative and RT-PCR-negative at baseline.
- The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 in participants seronegative and RT-PCR-negative at baseline.
- The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 with the onset at least 14 days after the second administration regardless of serostatus or RT-PCR status at baseline.
- The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 with the onset at least 14 days after the second administration regardless of serostatus or RT-PCR status at baseline.
- The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 regardless of serostatus or RT-PCR status at baseline.
- The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 regardless of serostatus or RT-PCR status at baseline.
- The first occurrence of asymptomatic SARS-CoV-2 infection beginning at least 14 days after the second administration in participants seronegative and RT-PCR-negative at baseline.
- The first occurrence of asymptomatic SARS-CoV-2 infection beginning at least 14 days after the second administration regardless of serostatus or RT-PCR status at baseline.

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Booster Vaccination Part

The efficacy endpoints were as follows:

- The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 with the onset at least 14 days after the booster vaccination in participants seronegative and RT-PCR-negative before the booster vaccination.
- The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 with the onset at least 14 days after the booster vaccination in participants seronegative and RT-PCR-negative before the booster vaccination.
- The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 after the booster vaccination in participants seronegative and RT-PCR-negative before the booster vaccination.
- The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 after the booster vaccination in participants seronegative and RT-PCR-negative before the booster vaccination.
- The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 with the onset at least 14 days after the booster vaccination regardless of serostatus and RT-PCR status before the booster vaccination.
- The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 with the onset at least 14 days after the booster vaccination regardless of serostatus and RT-PCR status before the booster vaccination.
- The first occurrence of SARS-CoV-2 RT-PCR-positive COVID-19 after the booster vaccination regardless of serostatus and RT-PCR status before the booster vaccination.
- The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 after the booster vaccination regardless of serostatus and RT-PCR status before the booster vaccination.
- The first occurrence of asymptomatic SARS-CoV-2 infection beginning at least 14 days after the booster vaccination in participants seronegative and RT-PCR-negative before the booster vaccination.
- The first occurrence of asymptomatic SARS-CoV-2 infection beginning at least 14 days after the booster vaccination regardless of serostatus and RT-PCR status before the booster vaccination.

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Safety Assessment:

A treatment-emergent adverse event (TEAE) was defined as AEs that occurred after the initial dose of the study intervention. Treatment-related AEs were defined as AEs considered to be "related" to the study intervention by the investigator.

Solicited AEs (solicited systemic AEs and solicited local AEs) were defined as any of the following AEs occurring within 7 days after each dose of the study intervention in this study. Solicited systemic AEs, solicited local AEs, and unsolicited AEs (events other than solicited systemic AEs or solicited local AEs) considered to be "related" to the study intervention were reported as solicited systemic treatment-related AEs, solicited local treatment-related AEs, and unsolicited treatment-related AEs, respectively.

- Solicited systemic AEs
  - Fever
  - Nausea/vomiting
  - Diarrhea
  - Headache
  - Fatigue
  - Myalgia
- Solicited local AEs
  - Pain
  - Erythema/redness
  - Induration
  - Swelling

Medically attended AE was defined as an AE that resulted in a visit to/from a healthcare professional (eg, staff from hospital, emergency room [ER], home, etc.) because of the AE.

Adverse events of special interest of S-268019 were defined as potential immune-mediated diseases.

Serious AEs, MAAEs, and AESIs were collected from the date of signing the ICF until the end-of-study/early discontinuation examination, and other AEs were collected from the date of signing the informed consent until 28 days after the second

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administration/early discontinuation examination. Physical examination results, vital signs, and laboratory test results were also assessed in this study.

The investigator or subinvestigator assessed the severity of solicited AEs reported during the study by referring to the Food and Drug Administration (FDA) guidance. The severity of unsolicited AEs and SAEs was assessed and classified into one of the 5 categories.

Pharmacokinetics Assessment:
Pharmacokinetics are not evaluated in this study.

Statistical Methods:

Immunogenicity Assessments:

Primary Vaccination Part

For the primary immunogenicity endpoint, the GMTR and its two-sided 95% confidence interval (CI) were estimated by back transformation of the difference (S-268019-b − ChAdOx1 nCoV-19) and its 95% CI which were obtained using analysis of covariance (ANCOVA) model fitted on the log-transformed titers. The model included intervention group as a fixed effect as well as age (continuous) as a covariate. The superiority of S-268019-b to the active control vaccine for GMT was to be established if the lower limit of the two-sided 95% CI for GMTR was greater than one.

For the key secondary endpoint, the 95% CI for the seroconversion rate was calculated using the Clopper-Pearson method. The difference in seroconversion rates for SARS-CoV-2 NAb between S-268019-b and the active control group, and its two-sided 95% CI were provided by Farrington-Manning method for the non-inferiority test. Non-inferiority of S-268019-b to the active control vaccine for seroconversion rate was to be established if the lower limit of the two-sided 95% CI for the difference in seroconversion rate was greater than a non-inferiority margin of −10%.

The analyses of the primary and key secondary endpoints were repeated for the subgroups based on age (18 to 39 years, 40 to 64 years, and ≥ 65 years, or 18 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 64 years, and ≥ 65 years), baseline body mass index (BMI) (< 30 kg/m^2 and ≥ 30 kg/m^2), and sex (male and female).

For the secondary immunogenicity endpoints, GMTs, GMFRs, and their 95% CIs at each visit were summarized by intervention group. The 95% CIs were calculated

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based on the *t* distribution of the natural log-transformed values of GMTs or GMFRs, then back transformed to the original scale for presentation. GMTRs, seroconversion rates, and their 95% CIs at each visit were estimated as described above and were presented by intervention group.

Booster Vaccination Part

For the primary endpoints in the booster vaccination part, the log-transformed titers on Day 57 and Day 239 in participants who received the third administration of S-268019-b in the S-268019-b group were compared using a paired t-test to estimate the GMTR (post-booster to post-primary series) along with the 95% CI for non-inferiority test. Furthermore, the difference in the seroconversion rate on Day 57 and the seroresponse rate on Day 239 was calculated along with the 95% CI using a restricted maximum likelihood estimation (RMLE-based) test for non-inferiority for paired binary data. Only when the non-inferiority is demonstrated for the GMT and seroresponse rate, the superiority of the GMT of the SARS-CoV-2 NAb titer on Day 239 to that on Day 57 was to be tested. The seroresponse rate was defined as the percentage of participants with a ≥ 4-fold increase in postvaccination antibody titer from the level before the third administration of the study intervention.

For the secondary endpoints in the booster vaccination part, the GMT at each visit after the third administration of the study intervention and the GMFR comparing to that before the third administration of the study intervention along with their 95% CIs were summarized by previous intervention group. The GMTR on Day 57 to that of each visit after the third administration and the 95% CI were computed for each previous intervention group. The difference between the seroconversion rate on Day 57 and the seroresponse rate, and the 95% CI were computed for each previous intervention group.

Efficacy Analyses:

For the efficacy endpoints, the number of cases, the incidence rate, and their 95% CIs as of the data cutoff date were calculated for each parameter. Vaccine efficacy (VE) of S-268019-b relative to ChAdOx1 nCoV-19 was estimated as (1 − RR)×100%, where RR was the relative risk. The cumulative incidences were presented using the Kaplan-Meier method.

Safety Analyses:

The number and percentage of participants who had solicited local AEs and systemic AEs within 7 days after each vaccination were summarized by intervention group.

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The number and percentage of participants with unsolicited AEs were summarized by intervention group for all AEs and treatment-related AEs.

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

Pharmacokinetic Analyses:

Pharmacokinetics were not evaluated in this study.

Summary of Results:

Demographics:

In the Immunogenicity Subset, the median age was 45.0 years in the S-268019-b group and 46.0 years in the active control group. The proportion of elderly participants (≥ 65 years) was 4.3% in the S-268019-b group and 4.5% in the active control group. The proportion of female participants was 34.5% in the S-268019-b group and 35.1% in the active control group. No substantial differences were observed in demographics or the other baseline characteristics between intervention groups.

In the Immunogenicity Subset for Booster Vaccination, the median age was 48.0 years. The proportion of elderly participants (≥ 65 years) was 4.1%. The proportion of female participants was 35.0%. Demographics and other baseline characteristics were similar to those in the Immunogenicity Subset. There were no substantial differences between participants who previously received S-268019-b and participants who previously received the active control vaccine.

Immunogenicity:

Primary Endpoint for Primary Vaccination

The GMTs of SARS-CoV-2 NAb 28 days after the second administration were 19.92 and 3.63 in the S-268019-b group and the active control group, respectively. The GMTR (S-268019-b/ChAdOx1 nCoV-19) was 5.48 (two-sided 95% CI: 5.01 to 6.00). The superiority of S-268019-b to ChAdOx1 nCoV-19 vaccine for the primary endpoint was demonstrated. The result of the Wilcoxon rank sum test was significant (two-sided p-value < 0.0001), supporting the superiority of S-268019-b to ChAdOx1 nCoV-19.

For the purpose of standardization of neutralizing activity of anti-SARS-CoV-2 antibodies among different vaccines, NAb titers were converted to the international standard units (IU/mL) of the WHO International Standards for anti-SARS-CoV-2

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immunoglobulin. The GMTs 28 days after the second administration were 198 IU/mL and 36 IU/mL in the S-268019-b group and the active control group, respectively.

In the sensitivity analysis using the data measured at [redacted], the GMTR (S-268019-b/ChAdOx1 nCoV-19) was 7.39 with the lower limit of the 95% CI of 6.55. In addition, the result of the Wilcoxon rank sum test was significant (two-sided p-value < 0.0001). These results supported the result of the primary analysis.

This was supported by the analyses in all subgroups based on age, BMI, and sex.

Key Secondary Endpoint for Primary Vaccination

The seroconversion rates for SARS-CoV-2 NAb 28 days after the second administration were 91.1% and 8.2% in the S-268019-b group and the active control group, respectively. The difference in the seroconversion rates was 83.0% (two-sided 95% CI: 76.8% to 89.1%). The lower limit of the two-sided 95% CI for the difference in seroconversion rates was greater than the non-inferiority margin of −10%, demonstrating non-inferiority of S-268019-b to ChAdOx1 nCoV-19 with the multiplicity adjustment by a fixed sequence procedure. This was supported by the analyses in all subgroups based on age, BMI, and sex.

In the sensitivity analysis using the data measured at [redacted], the difference in the seroconversion rates (S-268019-b – ChAdOx1 nCoV-19) was 32.8% (95% CI: 27.8% to 37.9%). These results supported the result of the primary analysis.

Secondary Endpoints for Primary Vaccination

In the S-268019-b group, the GMTs of SARS-CoV-2 NAb at baseline, on Days 29, 43, 57, 97, 211, and 393 were 2.61, 3.02, 37.90, 19.92, 10.42, 3.88, and 4.55, respectively. The GMFRs on Days 29, 43, 57, 97, 211, and 393 were 1.16, 14.66, 7.73, 4.04, 1.49, and 1.74, respectively. In the active control group, the GMTs of SARS-CoV-2 NAb at baseline, on Days 29, 43, 57, 97, 211, and 393 were 2.59, 3.05, 4.47, 3.63, 3.45, 3.17, and 3.50, respectively. The GMFRs on Days 29, 43, 57, 97, 211, and 393 were 1.17, 1.71, 1.40, 1.33, 1.22, and 1.40, respectively. The GMTRs (S-268019-b/ChAdOx1 nCoV-19) on Days 29, 43, 57, 97, 211, and 393 were 0.99, 8.47, 5.48, 3.03, 1.23, and 1.31, respectively.

In the S-268019-b group, the seroconversion rates for SARS-CoV-2 NAb on Days 29, 43, 57, 97, 211, and 393 were 5.2%, 96.7%, 91.1%, 67.2%, 13.4%, and 11.4%, respectively. In the active control group, the seroconversion rates for SARS-CoV-2

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NAb on Days 29, 43, 57, 97, 211, and 393 were 4.0%, 17.5%, 8.2%, 6.8%, 5.0%, and 12.1%, respectively.

In the S-268019-b group, the GMTs of anti-SARS-CoV-2 S-protein (S1/S2) IgG antibodies at baseline, on Days 29, 43, 57, 97, 211, and 393 were 2.56, 29.90, 597.51, 370.05, 203.52, 90.68, and 72.91, respectively. The GMFRs on Days 29, 43, 57, 97, 211, and 393 were 11.68, 237.70, 149.57, 83.09, 35.41, and 27.86, respectively. In the active control group, the GMTs of anti-SARS-CoV-2 S-protein (S1/S2) IgG antibodies at baseline, on Days 29, 43, 57, 97, 211, and 393 were 2.60, 37.28, 89.02, 77.92, 56.97, 29.45, and 21.08, respectively. The GMFRs on Days 29, 43, 57, 97, 211, and 393 were 14.10, 33.47, 29.30, 21.58, 10.81, and 7.98, respectively. The GMTRs (S-268019-b/ChAdOx1 nCoV-19) on Days 29, 43, 57, 97, 211, and 393 were 0.80, 6.70, 4.75, 3.58, 3.09, and 3.48, respectively.

In the S-268019-b group, the seroconversion rates for anti-SARS-CoV-2 S-protein (S1/S2) IgG antibody titer on Days 29, 43, 57, 97, 211, and 393 were 88.7%, 99.6%, 99.8%, 99.6%, 98.3%, and 97.7%, respectively. In the active control group, the seroconversion rates for anti-SARS-CoV-2 S-protein (S1/S2) IgG antibody titer on Days 29, 43, 57, 97, 211, and 393 were 90.6%, 98.3%, 98.2%, 95.5%, 83.4%, and 72.7%, respectively.

Primary Endpoint for Booster Vaccination

In participants who were vaccinated with S-268019-b for both primary and booster vaccinations, the GMTs of SARS-CoV-2 NAb on Day 57 and Day 239 (28 days after the booster vaccination) were 19.31 and 128.00, respectively. The GMTR (Day 239/Day 57) was 6.60 (95% CI: 5.89 to 7.38). The seroconversion/seroresponse rates for SARS-CoV-2 NAb on Day 57 and Day 239 were 90.5% and 96.9%, respectively. The difference in seroconversion/seroresponse rates (Day 239 – Day 57) was 6.2% (95% CI: 2.2% to 10.6%). Based on these results, it was demonstrated that the immunogenicity 28 days after the booster vaccination with S-268019-b was non-inferior to that 28 days after the second administration with S-268019-b.

Secondary Endpoints for Booster Vaccination

In participants previously vaccinated with S-268019-b, the GMTs of SARS-CoV-2 NAb on Days 211, 239, 302, and 393 were 3.66, 128.00, 81.45, and 50.75, respectively. The GMFRs on Days 239, 302, and 393 were 34.46, 22.70, and 13.89, respectively. In participants previously vaccinated with ChAdOx1 nCoV-19, the GMTs of SARS-CoV-2 NAb on Days 211, 239, 302, and 393 were 3.11, 48.67, 22.58, and 14.67, respectively. The GMFRs on Days 239, 302, and 393 were 15.64,

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7.55, and 4.87, respectively. The GMTRs (previous vaccine: S-268019-b/previous vaccine: ChAdOx1 nCoV-19) on Days 239, 302, and 393 were 2.68, 3.50, and 3.51, respectively.

In participants previously vaccinated with S-268019-b, the GMTRs of SARS-CoV-2 NAb on Days 239, 302, and 393 compared to the GMT on Day 57 were 6.60, 4.32, and 2.60, respectively. In participants previously vaccinated with ChAdOx1 nCoV-19, the GMTRs on Days 239, 302, and 393 compared to the GMT on Day 57 were 13.28, 6.27, and 4.02, respectively.

In participants previously vaccinated with S-268019-b, the seroresponse rates for SARS-CoV-2 NAb on Days 239, 302, and 393 were 96.9%, 98.3%, and 93.9%, respectively. In participants previously vaccinated with ChAdOx1 nCoV-19, the seroresponse rates for SARS-CoV-2 NAb on Days 239, 302, and 393 were 96.0%, 89.9%, and 72.9%, respectively. In participants previously vaccinated with S-268019-b, the differences in seroresponse rate from the seroconversion rate on Day 57 were 6.2%, 7.8%, and 2.1% on Day 239, Day 302, and Day 393, respectively. In participants previously vaccinated with ChAdOx1 nCoV-19, the differences in seroresponse rate from the seroconversion rate on Day 57 were 88.0%, 82.8%, and 65.2% on Day 239, Day 302, and Day 393, respectively.

In participants previously vaccinated with S-268019-b, the GMTs of anti-SARS-CoV-2 S-protein (S1/S2) IgG antibodies on Days 211, 239, 302, and 393 were 86.60, 2702.27, 1858.04, and 880.14, respectively. The GMFRs on Days 239, 302, and 393 were 31.13, 21.82, and 10.11, respectively. In participants previously vaccinated with ChAdOx1 nCoV-19, the GMTs of anti-SARS-CoV-2 S-protein (S1/S2) IgG antibodies on Days 211, 239, 302, and 393 were 29.02, 1083.36, 402.54, and 200.13, respectively. The GMFRs on Days 239, 302, and 393 were 37.34, 15.78, and 6.80, respectively. The GMTRs (previous vaccine: S-268019-b/previous vaccine: ChAdOx1 nCoV-19) on Days 239, 302, and 393 were 2.53, 4.52 and 4.46, respectively.

In participants previously vaccinated with S-268019-b, the GMTR of anti-SARS-CoV-2 S-protein (S1/S2) IgG antibodies on Days 239, 302, and 393 compared to the GMT on Day 57 were 7.72, 5.41, and 2.49, respectively. In participants previously vaccinated with ChAdOx1 nCoV-19, the GMTRs on Days 239, 302, and 393 compared to the GMT on Day 57 were 13.73, 5.50, and 2.45, respectively.

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In participants previously vaccinated with S-268019-b, the seroresponse rates for anti-SARS-CoV-2 S-protein (S1/S2) IgG antibodies on Days 239, 302, and 393 were 95.8%, 96.5%, and 87.2%, respectively. In participants previously vaccinated with ChAdOx1 nCoV-19, the seroresponse rates for anti-SARS-CoV-2 S-protein (S1/S2) IgG antibodies on Days 239, 302, and 393 were 95.4%, 92.4%, and 72.0%, respectively. In participants previously vaccinated with S-268019-b, the differences in seroresponse rate from the seroconversion rate on Day 57 were −3.9%, −2.6%, and −12.4% on Day 239, Day 302, and Day 393, respectively. In participants previously vaccinated with ChAdOx1 nCoV-19, the differences in seroresponse rate from the seroconversion rate on Day 57 were −2.3%, −6.9%, and −26.3% on Day 239, Day 302, and Day 393, respectively.

Exploratory Immunogenicity Assessments

The data show that the interferon gamma (IFN-γ)-producing cells that respond to the S-268019-b and ChAdOx1 nCoV-19 exist even about 6 months after the primary vaccination.

S-268019-b and ChAdOx1 nCoV-19 induced a higher percentage of Th1 cells (which produce IFN-γ or interleukin [IL]-2) than that of Th2 cells (which produce IL-4 or IL-5) after each vaccination.

Efficacy:

COVID-19 with the Onset at Least 14 Days After the Second Administration

The incidence rate of the first occurrence of RT-PCR-positive COVID-19 with the onset at least 14 days after the second administration was 192.70 per 1000 person-years (95% CI: 145.95 to 249.67) in the S-268019-b group and 207.43 per 1000 person-years (95% CI: 158.67 to 266.45) in the active control group. The VE of S-268019-b relative to ChAdOx1 nCoV-19 was 7.1% (95% CI: −35.5% to 36.4%). No severe COVID-19 with the onset at least 14 days after the second administration was observed in either intervention group.

COVID-19 After the First Administration

The incidence rate of the first occurrence of RT-PCR-positive COVID-19 after the first administration was 213.17 per 1000 person-years (95% CI: 168.23 to 266.43) in the S-268019-b group and 241.33 per 1000 person-years (95% CI: 193.29 to 297.68) in the active control group. The VE of S-268019-b relative to ChAdOx1 nCoV-19 was 11.7% (95% CI: −21.4% to 35.9%). Severe COVID-19 was reported in 2 participants in the S-268019-b group. One participant was positive for SARS-CoV-2

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RT-PCR test on Day 1 (prevaccination). Another participant developed COVID-19 within 14 days after the administration (Day 11).

Asymptomatic SARS-CoV-2 Infection Beginning at Least 14 Days after the Second Administration

The incidence rate of asymptomatic SARS-CoV-2 infection beginning at least 14 days after the second administration was 422.95 per 1000 person-years (95% CI: 348.25 to 508.92) in the S-268019-b group and 374.44 per 1000 person-years (95% CI: 304.66 to 455.42) in the active control group. The VE of S-268019-b relative to ChAdOx1 nCoV-19 was −13.0% (95% CI: −49.4% to 14.5%).

COVID-19 with the Onset at Least 14 Days After the Booster Vaccination

The incidence rate of the first occurrence of RT-PCR-positive COVID-19 with the onset at least 14 days after the booster vaccination was 198.29 per 1000 person-years (95% CI: 127.05 to 295.04) in participants previously vaccinated with S-268019-b, and 160.70 per 1000 person-years (95% CI: 100.71 to 243.31) in participants previously vaccinated with ChAdOx1 nCoV-19. The VE in participants previously vaccinated with S-268019-b relative to that in participants previously vaccinated with ChAdOx1 nCoV-19 was −23.4% (95% CI: −130.8% to 33.7%). No severe COVID-19 with the onset at least 14 days after the booster vaccination was observed.

COVID-19 After the Booster Vaccination

The incidence rate of the first occurrence of RT-PCR-positive COVID-19 after the booster vaccination was 189.59 per 1000 person-years (95% CI: 122.69 to 279.87) in participants previously vaccinated with S-268019-b, and 154.33 per 1000 person-years (95% CI: 97.83 to 231.57) in participants previously vaccinated with ChAdOx1 nCoV-19. The VE in participants previously vaccinated with S-268019-b relative to that in participants previously vaccinated with ChAdOx1 nCoV-19 was −22.8% (95% CI: −126.5% to 33.1%). No severe COVID-19 was observed after the booster vaccination.

Asymptomatic SARS-CoV-2 Infection Beginning at Least 14 Days after the Booster Vaccination

The incidence rate of asymptomatic SARS-CoV-2 infection beginning at least 14 days after the booster vaccination was 365.73 per 1000 person-years (95% CI: 265.74 to 490.98) in participants previously vaccinated with S-268019-b and 442.10 per 1000 person-years (95% CI: 337.37 to 569.07) in participants previously vaccinated with ChAdOx1 nCoV-19. The VE in participants previously vaccinated with S-268019-b

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relative to that in participants previously vaccinated with ChAdOx1 nCoV-19 was 17.3% (95% CI: −24.1% to 45.2%).

Genome of SARS-CoV-2

A total of 70 genome data of SARS-CoV-2, including 2 for "unanalyzable", were obtained in this study (56 for the primary vaccination part, 14 for the booster vaccination part). For the primary vaccination part, the most common genome types of SARS-CoV-2 were BA. 5 (53.6% [15 of 28] in the S-268019-b group, 32.1% [9 of 28] in the active control group). The other genome types of SARS-CoV-2 were either BA.1 lineage or BA.2 lineage, except for one that was "unanalyzable". For the booster vaccination part, all genome types of SARS-CoV-2 were BA. 5 (100.0% [7of 7] in participants previously vaccinated with S-268019-b, 85.7% [6 of 7] in participants previously vaccinated with ChAdOx1 nCoV-19), except for one that was "unanalyzable".

Safety:

Adverse Events

In the primary vaccination part of this study, AEs were reported in 94.3% (576 of 611) of participants in the S-268019-b group and 93.6% (571 of 610) of participants in the active control group. Most of them were considered related to the study intervention.

In the booster vaccination part, AEs were reported in 90.9% (328 of 361) of participants previously vaccinated with S-268019-b, and in 86.5% (326 of 377) of participants previously vaccinated with ChAdOx1 nCoV-19. Most of them were considered related to the study intervention.

Solicited Adverse Events

All solicited systemic and local AEs were considered related to the study intervention.

In the primary vaccination part of this study, most solicited AEs were Grade 1 or Grade 2. No Grade 5 solicited AEs were reported in this study. After the first administration, a Grade 4 solicited AE (fever) was reported in 1 participant (0.2%) in each intervention group. No Grade 4 solicited AEs were reported after the second administration.

Solicited systemic AEs were reported in 73.2% (447 of 611) of participants in the S-268019-b group and 80.5% (491 of 610) of participants in the active control group.

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The most common solicited systemic AE was fatigue in both intervention groups in both cases of the first and second administration.

Solicited local AEs were reported in 90.8% (555 of 611) of participants in the S-268019-b group and 85.1% (519 of 610) of participants in the active control group. The most common solicited local AE was pain in both intervention groups in both cases of the first and second administration.

The incidences of solicited systemic AEs after the first administration were generally higher in the active control group than in the S-268019-b group. However, the incidences of solicited systemic AEs after the second administration were generally higher in the S-268019-b group than in the active control group. The incidences of solicited local AEs after the first administration were generally comparable between intervention groups. However, the incidences of solicited local AEs after the second administration were generally higher in the S-268019-b group than in the active control group.

In the booster vaccination part, most solicited AEs were Grade 1 or Grade 2. No Grade 4 or Grade 5 solicited AEs were reported after the booster vaccination.

Solicited systemic AEs were reported in 73.4% (265 of 361) of participants previously vaccinated with S-268019-b, and in 61.3% (231 of 377) of participants previously vaccinated with ChAdOx1 nCoV-19. The most common solicited systemic AE was fatigue in both participants previously vaccinated with S-268019-b and with ChAdOx1 nCoV-19.

Solicited local AEs were reported in 83.4% (301 of 361) of participants previously vaccinated with S-268019-b, and in 78.8% (297 of 377) of participants previously vaccinated with ChAdOx1 nCoV-19. The most common solicited local AE was pain in both participants previously vaccinated with S-268019-b and with ChAdOx1 nCoV-19.

The incidences of solicited systemic and local AEs after the booster vaccination were generally higher in participants previously vaccinated with S-268019-b than in participants previously vaccinated with ChAdOx1 nCoV-19.

Unsolicited Adverse Events

In the primary vaccination part of this study, unsolicited AEs were reported in 26.7% (163 of 611) of participants in the S-268019-b group and 22.3% (136 of 610) of participants in the active control group. Unsolicited AEs related to the study

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intervention were reported in 34 participants (5.6%) in the S-268019-b group and 26 participants (4.3%) in the active control group. There was no meaningful difference in incidences of unsolicited AEs between intervention groups.

In the booster vaccination part, unsolicited AEs were reported in 11.1% (40 of 361) of participants previously vaccinated with S-268019-b, and in 12.2% (46 of 377) of participants previously vaccinated with ChAdOx1 nCoV-19. Unsolicited AEs related to the study intervention were reported in 11 participants (3.0%) who were previously vaccinated with S-268019-b, and in 3 participants (0.8%) who were previously vaccinated with ChAdOx1 nCoV-19. There was no meaningful difference in incidences of unsolicited AEs regardless of type of the previous vaccine.

Deaths and Other Serious Adverse Events

The vaccination with S-268019-b or ChAdOx1 nCoV-19 was generally well-tolerated. There were no deaths in this study. In the primary vaccination part, nonfatal SAEs were reported in 11 participants (1.8%) in the S-268019-b group and in 8 participants (1.3%) in the active control group. In the booster vaccination part, nonfatal SAEs were reported in 3 participants (0.8%) who were previously vaccinated with S-268019-b and in 8 participants (2.1%) who were previously vaccinated with ChAdOx1 nCoV-19. None of the SAEs were considered to be related to the study intervention by the investigators.

Adverse Events of Special Interest

In the primary vaccination part, an AESI was reported in 1 participant (0.2%) in the active control group (polymyalgia rheumatica). The event was considered to be related to the study vaccine. No AESIs were reported in the booster vaccination part.

Medically Attended Adverse Events

In the primary vaccination part, MAAEs were reported in 15.5% (95 of 611) of participants in the S-268019-b group and in 14.3% (87 of 610) of participants in the active control group. Medically attended AEs related to the study intervention were reported 6 participants (1.0%) in the active control group only. In the booster vaccination part, MAAEs were reported in 6.4% (23 of 361) of participants previously vaccinated with S-268019-b and 9.0% (34 of 377) of participants previously vaccinated with ChAdOx1 nCoV-19. No MAAEs related to the study intervention were reported in the booster vaccination part.

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Adverse Events Leading to Discontinuation of Study Intervention

In the primary vaccination part, AEs leading to discontinuation of study intervention were reported in 1 participant (0.2%) in the S-268019-b group (cerebral haemorrhage) and 1 participant (0.2%) in the active control group (cough and non-cardiac chest pain). These events were considered to be not related to the study vaccine by the investigator. The booster vaccination part consisted of participants who received the booster vaccination and, therefore, AEs leading to discontinuation of study intervention were not assessed in the booster vaccination part.

Vital Signs

No abnormal findings in vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) were found in either intervention group. The means of the data were within the reference ranges in both intervention groups at all time points after administration of the study vaccines.

Pharmacokinetics:
Pharmacokinetics are not evaluated in this study.

CONCLUSIONS
The primary objective of this study was to demonstrate the superiority of the immunogenicity of the primary vaccination with S-268019-b as compared to the ChAdOx1 nCoV-19. The immunogenicity of S-268019-b assessed by GMTs of SARS-CoV-2 NAb 28 days after the second administration was superior to the immunogenicity of ChAdOx1 nCoV-19. The seroconversion rate for SARS-CoV-2 NAb 28 days after the second administration of S-268019-b was non-inferior to that of ChAdOx1 nCoV-19. The GMT and seroconversion rate for anti-SARS-CoV-2 S-protein (S1/S2) IgG antibodies were generally higher in the S-268019-b group than in the active control group (ChAdOx1 nCoV-19).

The booster vaccination with S-268019-b effectively increased SARS-CoV-2 NAb titer. In participants previously vaccinated with S-268019-b, the lower limits of the 95% CIs of the GMTR and the difference in seroconversion/seroresponse rates between Day 57 (28 days after the second administration) and Day 239 (28 days after the booster vaccination) exceeded the pre-defined non-inferiority limits (0.67 and −10%, respectively). In addition, the lower limit of the 95% CI of the GMTR exceeded the pre-defined superiority limit of 1.0. The booster vaccination with S-268019-b increased SARS-CoV-2 NAb titer also in participants previously vaccinated with ChAdOx1 nCoV-19. However, the GMTs and seroresponse rates for

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SARS-CoV-2 NAb were higher in participants previously vaccinated with S-268019-b than in participants previously vaccinated with ChAdOx1 nCoV-19.

There were some differences in the incidence rates of SARS-CoV-2 RT-PCR-positive COVID-19 and asymptomatic SARS-CoV-2 infection after the primary vaccination between the S-268019-b group and the active control group. However, this study was not designed to have sufficient power to detect the statistically significant difference in VE, and the 95% CI of the relative VE included zero. Therefore, no definitive conclusion can be drawn about VE of S-268019-b relative to ChAdOx1 nCoV-19. Similarly, no definitive conclusion can be drawn about efficacy of booster vaccination with S-268019-b in participants who received different vaccines as the primary vaccination.

The primary vaccination with S-268019-b and the booster vaccination with S-268019-b were well-tolerated. There were no deaths and no SAEs related to the study intervention during the study. When vaccinating with S-268019-b, the incidences of solicited AEs generally increased from the first administration to the second administration. On the other hand, the incidences of solicited AEs generally decreased from the first administration to the second administration when vaccinating with ChAdOx1 nCoV-19. These results are consistent with the previous studies of ChAdOx1 nCoV-19 and Nuvaxovid, suggesting that the recombinant protein subunit vaccines have solicited AE profiles different from those of virus vector vaccines. The incidence of unsolicited AEs was low, and no clinically meaningful differences were observed between S-268019-b and ChAdOx1 nCoV-19.

In conclusion, the data obtained from this study fully support the favorable immunogenicity profile and acceptable safety profile of S-268019-b. The VE of S-268019-b relative to ChAdOx1 nCoV-19 has remained inconclusive. However, considering the fact that there is a correlation between SARS-CoV-2 NAb titer and VE, the VE of S-268019-b is expected to be comparable or greater than that of ChAdOx1 nCoV-19. The primary and booster vaccinations with S-268019-b were considered to be safe, and no significant safety issues were identified.

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