2. SYNOPSIS

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Study Title:
A Phase 2/3, Randomized, Observer-Blind, Active-Controlled Study to Evaluate the Immunogenicity of a Booster Dose of S-268019 or COMIRNATY

Investigators and Study Centers:
This was a single-center study conducted in Japan.

Publication (reference): Not applicable.

Studied Period:
From 03 Dec 2021 to 24 Jul 2023 (the date of the last-participant-last-visit)

Phase of Development: Phase 2/3

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To verify the noninferiority of the immunogenicity of S-268019-b as a booster injection compared to COMIRNATY.	• SARS-CoV-2 neutralizing antibody titer on Day 29 – Geometric mean titer (GMT) – Seroresponse rate
Secondary	
• To assess the immunogenicity other than the primary endpoint after booster injection of S-268019-b.	• The following items for SARS-CoV-2 neutralizing antibody and anti-spike protein immunoglobulin G (IgG) antibody other than the primary endpoints – GMT – Geometric mean fold rise (GMFR) – Seroresponse rate – Seroprotection rate
• To assess the safety after booster injection of S-268019-b or COMIRNATY.	• The incidence of adverse events (AEs)/treatment-related AEs/serious adverse events (SAEs)/solicited AEs/medically-attended adverse events (MAAEs)/adverse events of special interest (AESIs), vital signs, laboratory test values, and electrocardiograms (ECGs)

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• To investigate the clinical efficacy after booster injection of S-268019-b or COMIRNATY.	• The following items ≥ 14 days after administration of S-268019-b or COMIRNATY – Number of participants with symptomatic COVID-19 – Number of asymptomatic participants • The following items after administration of S-268019-b or COMIRNATY – Number of participants with symptomatic COVID-19 – Number of asymptomatic participants
• To assess the immunogenicity of the additional booster injection (second booster injection) with S-268019-b in participants who received the first booster injection with S-268019-b or COMIRNATY.	• The GMT and seroresponse rate of SARS-CoV-2 neutralizing antibody and the GMT for anti-spike protein IgG antibody.
• To assess the safety of the additional booster injection (second booster injection) with S-268019-b in participants who received the first booster injection with S-268019-b or COMIRNATY.	• The incidence of AEs/treatment-related AEs/SAEs/solicited AEs/MAAEs/AESIs
Exploratory	
• To explore other immunological indices.	• Cellular immunity – Cytokine-producing cell count – Human leukocyte antigen (HLA)-A genotyping • Type 1 helper T cells/Type 2 helper T cells balance (Th1/Th2 balance) – T cell cytokine assay • Assessment of neutralizing antibody titers against variants of interest (VOIs) and variants of concern (VOCs) • Assessment of immunity after booster vaccination – Analysis of functions and characteristics of antibody to SARS-CoV-2 and immune cells

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Methodology:

This study was a phase 2/3, single-center, randomized, observer-blinded, active-controlled study to evaluate noninferiority of the immunogenicity of S-268019-b compared to COMIRNATY and to assess safety of S-268019-b. A total of 206 participants (S-268019-b group: 102 participants; COMIRNATY group: 104 participants) aged 21 years or older who had completed vaccination with 2 injections of COMIRNATY were enrolled. The participants were randomized to the S-268019-b group or the COMIRNATY group at 1:1 ratio. The assignment of the participants was stratified by age (younger than 40 years and 40 years or older) and sex.

Participants who received an intramuscular injection of S-268019-b or COMIRNATY on Day 1 and were monitored for approximately 12 months. Participants who provided additional informed consent for the second booster injection additionally received a single intramuscular injection of S-268019-b on Day 365, and were monitored for approximately 6 months.

If SARS-CoV-2 infection was suspected in a participant after study intervention on Day 1 to the final visit (if COVID-19-related symptoms listed in the table below [see Efficacy Assessment] were observed), the participant was to make a COVID-19 Potential Illness Visit, and if the reverse transcription polymerase chain reaction (RT-PCR) test result was positive, the participant was to also make a COVID-19 Follow-up Visit 28 days after the COVID-19 Potential Illness Visit. The participants who had completed the COVID-19 Potential Illness Visit were to also make a COVID-19 Illness Visit if the investigator judged that additional testing was necessary (excluding the participants whose RT-PCR test result was negative at the COVID-19 Potential Illness Visit).

The study was composed of the following 3 periods:

- Screening period (Day −28 to Day 1 pre-injection):
  Participants who had provided informed consent were investigated and examined to confirm their eligibility for participation in the study. Before the study intervention on Day 1, those who were eligible to participate in the study were randomized to the S-268019-b group or the COMIRNATY group at 1:1 ratio.
- Evaluation period (Day 1 post-injection to Day 29):
  Participants who received 1 injection of the study intervention via intramuscular injection on Day 1, and underwent the post-injection investigations/examinations as scheduled. Participants also visited the study

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site on Days 2, 15, and 29 to undergo the scheduled investigations/examinations.

- Follow-up period (Day 30 to Day 365 [Day 30 to Day 547 if the study intervention was administered on Day 365]):
  Participants were visited the study site on Days 69, 183, and 365 to undergo the scheduled investigations/examinations. Participants who provided additional informed consent for the second booster injection received an additional booster injection of S-268019-b via intramuscular injection on Day 365, and visited the study site on Days 393, 433, and 547.

This final clinical study report (CSR) was prepared based on the results of final analyses using the data from all participants up to the final visit in the study.

Number of Participants (Planned and Analyzed):

Planned: 204 participants (to be randomized to the S-268019-b group or the COMIRNATY group at 1:1 ratio)

Randomized: 206 (102 in the S-268019-b group, 104 in the COMIRNATY group)

Analyzed for immunogenicity:

- Immunogenicity subset: 203 (101 in the S-268019-b group, 102 in the COMIRNATY group)
  - Immunogenicity subset for the participants who completed the second booster injection without infection history of SARS-CoV-2 up to the second booster injection (Day 365): 90 (43 in the S-268019-b group, 47 in the COMIRNATY group)
  - Immunogenicity subset for the participants who completed the second booster injection with infection history of SARS-CoV-2 up to the second booster injection (Day 365): 74 (39 in the S-268019-b group, 35 in the COMIRNATY group)

Analyzed for efficacy:

- Modified intent-to-treat (mITT) population: 203 (101 in the S-268019-b group, 102 in the COMIRNATY group)

Analyzed for safety:

- Safety analysis population: 204 (101 in the S-268019-b group, 103 in the COMIRNATY group)

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– Safety analysis population for the participants who completed the second booster injection: 165 (82 in the S-268019-b group, 83 in the COMIRNATY group)

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria
   - Male or female participants who were 20 years of age or older at the time of signing the informed consent form (ICF).
   - At least 6 months had passed after completion of the second injection with COMIRNATY.
2. Exclusion criteria
   - Tested positive for SARS-CoV-2 infection (as determined by SARS-CoV-2 antigen test) at screening.
   - Determined in the interview prior to the study intervention to have a history of SARS-CoV-2 infection.
   - Was having a fever of 37.5°C or higher on the day of study intervention.
   - Was receiving anticoagulation therapy, or had thrombocytopenia or coagulopathy.
   - Had a history of convulsion.
   - Current history of poorly controlled 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.
   - Immunosuppressed (immunocompromised, having AIDS, having received steroids and having received systemic immunosuppressants within 6 months prior to the study intervention, being treated for malignant tumor, being on 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, contraindicated participation in the study (except for pollinosis and atopic dermatitis).
   - Had experienced serious adverse reactions (including myocarditis and pericarditis) to COMIRNATY in the past.
   - Contraindicated to intramuscular injections or blood draws.

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- Previous SARS-CoV-2 vaccination with an approved or investigational product (except for COMIRNATY).
- Anti-SARS-CoV-2 monoclonal antibody, immunoglobulin preparations, blood products, or a blood transfusion within 3 months prior to the study intervention.

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

1. Test Product (S-268019-b)
   - 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

For the study intervention on Day 1, S-268019 injectable (containing S-910823) 40 μg/mL and S-268019 oil in water emulsion for injection 1 mL were mixed in a ratio of 1:1 (each 0.25 mL for 1 injection). One injection (0.5 mL mixture) of S-910823-b was given in the upper arm as an intramuscular injection.

For the study intervention on Day 365, S-268019 injectable (containing S-910823) 40 μg/mL and S-268019 oil in water emulsion for injection 0.9 mL were mixed in a ratio of 1:1 (each 0.25 mL for 1 injection). One injection (0.5 mL mixture) of S-910823-b was given in the upper arm as an intramuscular injection.

3. Packaging Lot Number

S-910823 (antigen): [redacted]

A-910823 (adjuvant) 1 mL: [redacted]

A-910823 (adjuvant) 0.9 mL: [redacted]

Duration of Treatment:

One day or two days (A single injection of the assigned study intervention was administered on Day 1 in the evaluation period. In addition to Day 1 of study intervention, a single injection of S-268019-b was administered on Day 365 in the follow-up period to those who consent to the second booster.)

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

1. Reference Therapy

COMIRNATY

2. Dose and Mode of Administration

COMIRNATY was diluted with 1.8 mL of physiological saline. One injection

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(0.3 mL) of COMIRNATY (containing 30 µg of tozinameran) was given in the upper arm as an intramuscular injection.

3. Packaging Lot Number [redacted]

Criteria for Evaluation:

Immunogenicity and Other Immunological Indices Assessment:

Noninferiority in immunogenicity of S-268019-b given as the first booster injection compared to COMIRNATY in participants who had completed vaccination with 2 injections of COMIRNATY was evaluated.

Efficacy Assessment:

Symptomatic COVID-19 was defined as a positive test result of RT-PCR and the presence of at least one of the following COVID-19-related symptoms, or fulfillment of the criteria of severe COVID-19. The COVID-19-related symptoms were tracked using an electronic patient reported outcome (ePRO) system in this study.

COVID-19-related symptoms	
Duration	Symptoms
No minimum duration defined	Fever (≥ 37.5°C), 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

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, heart rate ≥ 125 beats per minute, peripheral capillary oxygen saturation (SpO_2) ≤ 93% on room air at sea level, or PaO_2/FiO_2 < 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

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Participants without symptomatic COVID-19 who had tested positive for anti-SARS-CoV-2 nucleocapsid protein (N-protein) antibody specified in schedule of activities (SoA) were treated as asymptomatic COVID-19.

Safety Assessment:

Treatment-emergent adverse events (TEAEs) were defined as AEs that occurred after the study intervention. Treatment-related AEs were defined as AEs considered to be "related" to the study intervention by the treating physician.

Solicited AEs (solicited systemic AEs and solicited local AEs) were defined as any of the following AEs which occurred within 7 days after each 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
  - Arthralgia
  - Chills
- Solicited local AEs
  - Pain
  - Erythema/redness
  - Induration
  - Swelling

MAAE was defined as an AE that resulted in a visit to/from a health care professional (eg, staff from hospital, emergency room, home, etc.) because of the AE.

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

SAEs, 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 obtaining the informed consent until 28 days after the vaccination/early

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discontinuation examination. Physical examination results, vital signs, 12-lead ECGs, 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 as Grade 1 to 5 referring to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Statistical Methods:

Immunogenicity Analyses:

The following immunogenicity analyses for the first booster injection were performed for the immunogenicity subset. The analysis methods for primary and secondary immunogenicity endpoints for the first booster injection were as follows:

Primary immunogenicity endpoint:

- GMT and seroresponse rate (proportion of participants with a ≥ 4-fold rise from baseline) of SARS-CoV-2 neutralizing antibody titer on Day 29:
  The geometric mean titer ratio (GMTR) and the corresponding 95% CI were estimated by back transformation of the intervention difference (S-268019-b − COMIRNATY) and its 95% CI which were obtained using an analysis of covariance (ANCOVA) model fitted on the log-transformed titers. The model included intervention group as the fixed effect as well as age (continuous) and sex as the covariates. The difference in seroresponse rate on Day 29 between the intervention groups and the corresponding 95% CI were estimated by Farrington-Manning method.
  If the lower limit of the 95% CI for the GMTR (S-268019-b/COMIRNATY) was greater than 0.67 AND the lower limit of the 95% CI for the difference in seroresponse rate (S-268019-b − COMIRNATY) was greater than −10%, noninferiority of S-268019-b to COMIRNATY was to be confirmed. Only if noninferiority for both GMT and the seroresponse rate was confirmed, then superiority was to be tested. The superiority was to be confirmed if the lower bound of the 95% CI for the GMTR was greater than 1.

Secondary immunogenicity endpoints:

- GMT of SARS-CoV-2 neutralizing antibody at each time point except for Day 29:
  The GMT and the corresponding 95% CI were calculated by back transformation of the arithmetic mean and its 95% CI of the log-transformed

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titers for each study intervention group.
For log-transformed SARS-CoV-2 neutralizing antibody titer, the ANCOVA model using the study intervention group as the fixed effect, and age (continuous) and sex as the covariates was applied for each time point, the GMTR of the antibody between the study intervention groups and the 95% CI were estimated, and inter-group comparison was conducted.

- GMFR of SARS-CoV-2 neutralizing antibody titer at each time point:
  The GMFR and the corresponding 95% CI were calculated by back transformation of the arithmetic mean and its 95% CI of the change from baseline in log-transformed titers for each study intervention group.
  For the change from baseline in log-transformed SARS-CoV-2 neutralizing antibody titer, the ANCOVA model using the study intervention group as the fixed effect, and age (continuous) and sex as the covariates was applied for each time point, the ratio of the GMFR between the study intervention groups and the 95% CI were estimated, and inter-group comparison was conducted.
- Seroresponse rate of SARS-CoV-2 neutralizing antibody titer at each time point except for Day 29:
  The seroresponse rate of SARS-CoV-2 neutralizing antibody titer and its 95% CI were calculated at each time point for each study intervention group. The 95% CI for antibody titer seroresponse rate was calculated using the Clopper-Pearson method. The difference in the seroresponse rate and the 95% CI were estimated, and inter-group comparison was conducted.
- Seroprotection rate of SARS-CoV-2 neutralizing antibody titer at each time point:
  The seroprotection rate of the participants with a SARS-CoV-2 neutralizing antibody titer of ≥ 20 and the 95% CI were calculated at each time point for each study intervention group. The 95% CI for seroprotection rate was calculated using the Clopper-Pearson method. The difference in the seroprotection rate and the 95% CI were estimated, and inter-group comparison was conducted. The same analysis was conducted for the seroprotection rate of the participants with a SARS-CoV-2 neutralizing antibody titer of ≥ 10.
  The threshold titers defining the seroprotection rates (10 or 20) were decided on the basis of the SARS-CoV-2 neutralizing antibody titers in serum samples of convalescent patients.

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- GMT of anti-spike protein IgG antibody at each time point:
  The GMT and the corresponding 95% CI were calculated by back transformation of the arithmetic mean and its 95% CI of the log-transformed titers for each study intervention group.
  For log-transformed anti-spike protein IgG antibody titer, the ANCOVA model using the study intervention group as the fixed effect, and age (continuous) and sex as the covariates was applied for each time point, the GMTR of the antibody titer between the study intervention groups and the 95% CI were estimated, and inter-group comparison was conducted.
- GMFR of anti-spike protein IgG antibody titer at each time point:
  The GMFR and the corresponding 95% CI were calculated by back transformation of the arithmetic mean and its 95% CI of the change from baseline in log-transformed titers for each study intervention group.
  For the change from baseline in log-transformed anti-spike protein IgG antibody titer, the ANCOVA model using the study intervention group as the fixed effect, and age (continuous) and sex as the covariates was applied for each time point, the ratio of the GMFR between the study intervention groups and the 95% CI were estimated, and inter-group comparison was conducted.
- Seroresponse rate of anti-spike protein IgG antibody titer at each time point:
  The seroresponse rate of anti-spike protein IgG antibody titer and its 95% CI were calculated at each time point for each study intervention group. The 95% CI for antibody titer seroresponse rate was calculated using the Clopper-Pearson method. The difference in the seroresponse rate and the 95% CI were estimated, and inter-group comparison was conducted.
- Seroprotection rate of anti-spike protein IgG antibody titer at each time point:
  The seroprotection rate of the participants with an anti-spike protein IgG antibody titer of ≥ 3200 and the 95% CI were calculated at each time point for each study intervention group. The 95% CI for seroprotection rate was calculated using the Clopper-Pearson method. The difference in the seroprotection rate and the 95% CI were estimated, and inter-group comparison was conducted. The same analysis was conducted for the seroprotection rate of the participants with an anti-spike protein IgG antibody titer of ≥ 6400.
  The threshold titers defining the seroprotection rates (3200 or 6400) were decided on the basis of the anti-spike protein IgG antibody titers in serum samples of convalescent patients.

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The following immunogenicity analyses for second booster injection were performed for the immunogenicity subset. The analysis methods for secondary immunogenicity endpoints for the second booster injection were as follows:

Secondary immunogenicity endpoints:

- GMT of SARS-CoV-2 neutralizing antibody at each time point for participants who completed the second booster injection:
  The GMT and the corresponding 95% CI were calculated by back transformation of the arithmetic mean and its 95% CI of the log-transformed titers for each study intervention group. The analyses by with/without infection history of SARS-CoV-2 up to the second booster injection (Day 365) were performed.
- GMT of SARS-CoV-2 neutralizing antibody on Day 393:
  The immunogenicity of second booster injection was evaluated in comparison to that of first booster injection. Specifically, for the participants in the immunogenicity subset for the second booster injection, the paired-samples t-test for the noninferiority and superiority evaluation to compare GMTs between Day 29 and Day 393 was performed, and the GMTR and the corresponding 95% CI were calculated for each study intervention group. The analyses were performed for participants who completed the second booster injection without infection history of SARS-CoV-2 up to the second booster injection (Day 365). The noninferiority was confirmed if the lower bound of the 95% CI for the GMTR was greater than 0.67 and the superiority was confirmed if the lower bound of the 95% CI for the GMTR was greater than 1.0.
  In addition, the immunogenicity of second booster injection was evaluated in comparison to that of primary vaccination. Specifically, the noninferiority of the GMT on 28 days after the second booster injection in this study (Day 393) compared to the GMT of 28 days after the second injection of primary vaccination (Day 57) of the participants aged 64 years or younger who completed 2 injections of S-268019-b and included in the immunogenicity subset for primary analysis in a separate phase 3 study (Study 2025U0231) (hereinafter referred to the external control population) was evaluated. The GMTR and the corresponding 95% CI were estimated by back transformation of the intervention mean difference of the log-transformed titers for each study intervention group and its 95% CI as the noninferiority and superiority evaluation. The analyses were performed for participants who completed the second booster injection without infection history of SARS-CoV-2 up to the

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second booster injection (Day 365). The noninferiority was confirmed if the lower bound of the 95% CI for the GMTR was greater than 0.67 and the superiority was confirmed if the lower bound of the 95% CI for the GMTR was greater than 1.0.

- Seroresponse rate of SARS-CoV-2 neutralizing antibody titer on Day 393:
  The immunogenicity of second booster injection was evaluated in comparison to that of first booster injection. Specifically, for the participants in the immunogenicity subset for the second booster injection, the test for paired binary data was performed by estimating the difference and its 95% CI between the seroresponse rate on 28 days after the first booster injection (Day 29) and the seroresponse rate on 28 days after the second booster injection (Day 393) for SARS-CoV-2 neutralizing antibody titer for each study intervention group, and the noninferiority evaluation was performed. Seroresponse rate on Day 393 was defined as the proportion of participants with a ≥ 4-fold rise from titers before the second booster injection in SARS-CoV-2 neutralizing antibody titer. The analyses were performed for participants who completed the second booster injection without infection history of SARS-CoV-2 up to the second booster injection (Day 365). The noninferiority was confirmed if the lower bound of the 95% CI for the difference between the seroresponse rate was greater than −10%.
  In addition, the seroresponse rate of second booster injection was evaluated in comparison to the seroconversion rate of primary vaccination. Specifically, the noninferiority of the seroresponse rate on 28 days after the second booster injection (Day 393) in this study to the seroconversion rate on 28 days after the second injection of primary vaccination (Day 57) of the external control population was evaluated. The difference between the seroresponse rate on Day 393 in the study and the seroconversion rate on Day 57 of the external control population, and the corresponding 95% CI were estimated by Farrington-Manning method as the noninferiority evaluation for each study intervention group. The analyses were performed for participants who completed the second booster injection without infection history of SARS-CoV-2 up to the second booster injection (Day 365). The noninferiority was confirmed if the lower bound of the 95% CI for the difference between the rate was greater than −10%.

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- GMT of anti-spike protein IgG antibody at each time point:
  The GMT and the corresponding 95% CI were calculated by back transformation of the arithmetic mean and its 95% CI of the log-transformed titers for each study intervention group.
  For log-transformed anti-spike protein IgG antibody titer, the ANCOVA model using the study intervention group as the fixed effect, and age (continuous) and sex as the covariates was applied for each time point, the GMTR of the antibody titer between the study intervention groups and the 95% CI were estimated, and inter-group comparison was conducted.
  For participants who completed the second booster injection, for anti-spike protein IgG antibody at each time point, the GMT and the corresponding 95% CI were calculated by back transformation of the arithmetic mean and its 95% CI of the log-transformed titers for each study intervention group. The analyses by with/without infection history of SARS-CoV-2 up to the second booster injection (Day 365) were performed.

Efficacy Analyses:

The number of participants in the mITT population with symptomatic COVID-19 or asymptomatic COVID-19 confirmed 14 days or later after the study intervention with S-268019-b or COMIRNATY was tabulated for each study intervention group. The number of participants with symptomatic COVID-19 or asymptomatic COVID-19 confirmed after the study intervention with S-268019-b or COMIRNATY was also tabulated.

The incidence rate was calculated as the number of participants with an event divided by the total person-years at risk. The 95% CI was calculated using the exact method assuming Poisson distribution of events. Moreover, cumulative incidence was presented using the Kaplan-Meier method for each study intervention. Participants were censored at the time of last date of study participation, efficacy data cut-off date, administration of the approved vaccine, or the second booster injection of S-268019-b, whichever was earlier. The same analyses were performed for participants who had symptomatic COVID-19 or asymptomatic COVID-19 participants who were tested positive for anti-SARS-CoV-2 N-protein antibody test for the first time after the study intervention.

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Safety Analyses:

The following safety analyses were performed for the safety analysis population. The analyses of AE occurring after the first booster injection were based on the data collected from participants who did not receive the second booster injection, and the data before the second booter injection from the participants who received the second booster injection. The analyses of AE occurring after the second booster injection were based on the data collected after the second booter injection.

AEs were coded and classified by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1. The number and proportion of participants with AEs and its 95% CI were summarized by the study intervention group. The 95% CI for the incidence was calculated using the Clopper-Pearson method. The number of cases of these AEs was also tabulated. The number of participants with at least 1 AE leading to death, other SAEs, MAAEs, AESIs, treatment-related AEs, treatment-related AEs with an outcome of death, nonfatal treatment-related SAEs, treatment-related MAAEs, and treatment-related AESIs was similarly summarized. In addition, the data were summarized by severity, time to onset, and duration. Solicited systemic AEs were summarized by the AE name (fever, nausea/vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, and chills). Solicited local AEs were summarized by the AE name (pain, erythema/redness, induration, and swelling). The number and proportion of participants with solicited systemic/local AEs and its 95% CI were summarized by the study intervention group. The 95% CI for the incidence was calculated using the Clopper-Pearson method. The number of cases of these AEs was also tabulated. Treatment-related solicited systemic/local AEs were summarized in the same manner. In addition, the data were summarized by severity, time to onset, and duration.

The summary statistics for laboratory test results, vital signs, 12-lead ECG measurements, and their changes from baseline at each scheduled time point were presented for each study intervention group.

Summary of Results:

Demographics:

- In the immunogenicity subset, all participants were Asian, and the proportion of male participants was 70.3% in the S-268019-b group and 70.6% in the COMIRNATY group (in the same order hereinafter). The median age (min-max) was 30.0 (21-59) years and 31.5 (21-60) years. None of the participants were 65 years or older. The mean body mass index (BMI) (SD) was 23.24 (4.55) and 23.07 (4.73). There were no differences in the demographics and baseline

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characteristics of the immunogenicity subset between the study intervention groups.

- In the immunogenicity subset for the second booster injection of the S-268019-b group, all participants were Asian, and the proportion of male participants in total participants, male participants without infection history, and male participants with infection history was 74.4%, 76.7%, and 71.8%, respectively (in the same order hereinafter). The median age (min-max) was 30.5 (21-59) years, 33.0 (22-58) years, and 26.0 (21-59) years, respectively. The mean BMI (SD) was 23.06 (3.49), 23.29 (3.43), and 22.80 (3.58), respectively. There were no significant differences in the demographics or baseline characteristics of the immunogenicity subset for the second booster injection of S-268019-b group between the participants with infection history and without infection history.
  For the external control population, all participants were Asian, and the proportion of male participants was 65.9%. The median age (min-max) was 44.0 (20-64) years, and the mean BMI (SD) was 23.59 (4.36).
  There were no significant differences in the demographics or baseline characteristics between the participants in the S-268019-b or the COMIRNATY group of this study who had no history of SARS-CoV-2 infection up to the second booster injection (Day 365) and the external control population.

Immunogenicity:

Participants who Received the First Booster Injection on Day 1: Results up to the Second Booster Injection on Day 365:

- Primary Immunogenicity Endpoint
  The ANCOVA-estimated GMTR (95% CI) of SARS-CoV-2 neutralizing antibody (S-268019-b/COMIRNATY) was 1.14 (0.94 to 1.39) and the difference in seroresponse rate of SARS-CoV-2 neutralizing antibody titer (S-268019-b − COMIRNATY) was 0.0% (−5.9% to 5.9%). The lower limit of the 95% CI for the GMTR was greater than 0.67 (one-sided $p < 0.0001$), and that for the difference in seroresponse rate was greater than −10% (one-sided $p = 0.0004$). Therefore, the noninferiority of S-268019-b to COMIRNATY was demonstrated. The lower limit of the 95% CI for the GMTR was not greater than 1.0 (one-sided $p = 0.0971$). Therefore, the superiority of S-268019-b to COMIRNATY was not demonstrated.

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- Secondary Immunogenicity Endpoints
  - The GMT (95% CI) of SARS-CoV-2 neutralizing antibody was 5.47 (4.81 to 6.21) in the S-268019-b group and 6.65 (5.73 to 7.72) in the COMIRNATY group before the study vaccination (baseline). After 1 injection of the study intervention administered for the first booster injection, the GMT of SARS-CoV-2 neutralizing antibody increased from baseline at Day 29 and then gradually decreased until Day 365 in both groups; the GMTs (95% CIs) on Days 15, 29, 69, 183, and 365 were 127.57 (112.03 to 145.28), 124.97 (108.33 to 144.18), 76.10 (65.51 to 88.40), 49.60 (41.01 to 59.99), and 47.90 (34.60 to 66.31), respectively, in the S-268019-b group, and 139.48 (122.50 to 158.82), 109.70 (95.73 to 125.70), 68.85 (60.30 to 78.61), 32.85 (27.42 to 39.36), and 19.54 (15.48 to 24.67), respectively, in the COMIRNATY group.
  - The GMFRs (95% CIs) of SARS-CoV-2 neutralizing antibody titer in the S-268019-b group and the COMIRNATY group were 23.34 (20.23 to 26.92) and 20.77 (18.14 to 23.77), respectively, on Day 15, 22.86 (19.54 to 26.74) and 16.33 (14.22 to 18.76), respectively, on Day 29, 13.77 (11.64 to 16.29) and 10.06 (8.59 to 11.77), respectively, on Day 69, 8.73 (7.12 to 10.71) and 4.76 (3.96 to 5.72), respectively, on Day 183, and 9.19 (6.63 to 12.73) and 3.00 (2.42 to 3.71), respectively, on Day 365.
  - The seroresponse rates (95% CIs) of SARS-CoV-2 neutralizing antibody titer in the S-268019-b group and the COMIRNATY group were 100.0% (96.4% to 100.0%) and 99.0% (94.6% to 100.0%), respectively, on Day 15, 100.0% (96.4% to 100.0%) and 100.0% (96.4% to 100.0%), respectively, on Day 29, 97.9% (92.7% to 99.7%) and 93.8% (87.0% to 97.7%), respectively, on Day 69, 86.2% (77.1% to 92.7%) and 72.7% (62.2% to 81.7%), respectively, on Day 183, and 88.0% (75.7% to 95.5%) and 45.0% (32.1% to 58.4%), respectively, on Day 365.
  - The GMT (95% CI) of anti-spike protein IgG antibody was 1453.4 (1259.1 to 1677.8) in the S-268019-b group and 1808.2 (1546.8 to 2113.7) in the COMIRNATY group before the study vaccination (baseline). After 1 injection of the study intervention administered for the first booster injection, the GMT of anti-spike protein IgG antibody increased from baseline at Day 29 and then gradually decreased until Day 365 in both groups; the GMTs (95% CIs) on Days 15, 29, 69, 183, and 365 were 51200.0 (44471.9 to

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58945.9), 48464.8 (41429.9 to 56694.2), 13360.7 (11262.1 to 15850.4), 18466.1 (14933.3 to 22834.6), and 15758.6 (11512.0 to 21571.9), respectively, in the S-268019-b group, and 69725.6 (62340.0 to 77986.1), 55214.8 (49013.5 to 62200.7), 10404.3 (9200.8 to 11765.1), 13314.2 (11422.6 to 15519.0), and 7267.2 (5672.3 to 9310.7), respectively, in the COMIRNATY group.

– The GMFRs (95% CIs) of anti-spike protein IgG antibody titer in the S-268019-b group and the COMIRNATY group were 35.23 (29.76 to 41.70) and 38.25 (32.94 to 44.42), respectively, on Day 15, 33.35 (27.93 to 39.81) and 30.29 (25.92 to 35.39), respectively, on Day 29, 9.03 (7.47 to 10.93) and 5.60 (4.84 to 6.47), respectively, on Day 69, 12.30 (9.78 to 15.46) and 7.34 (6.02 to 8.94), respectively, on Day 183, and 11.16 (7.86 to 15.83) and 4.09 (3.09 to 5.41), respectively, on Day 365.
– The seroresponse rates (95% CIs) of anti-spike protein IgG antibody titer in the S-268019-b group and the COMIRNATY group were 100.0% (96.4% to 100.0%) and 100.0% (96.4% to 100.0%), respectively, on Day 15, 100.0% (96.4% to 100.0%) and 100.0% (96.4% to 100.0%), respectively, on Day 29, 89.7% (81.9% to 94.9%) and 82.5% (73.4% to 89.4%), respectively, on Day 69, 90.8% (82.7% to 95.9%) and 86.4% (77.4% to 92.8%), respectively, on Day 183, and 88.0% (75.7% to 95.5%) and 53.3% (40.0% to 66.3%), respectively, on Day 365.
– The interferon-gamma (IFN-γ)-producing cells that responded to the first booster injection with S-268019-b or COMIRNATY increased after the first booster injection.
– The first booster injection induced a higher percentage of Th1 cells (T cells which produce IFN-γ or interleukin [IL]-2) than that of Th2 cells (T cells which produce IL-4 or IL-5) in both groups (S-268019-b and COMIRNATY).

Participants who Received the First Booster Injection on Day 1 and the Second Booster Injection on Day 365:

- Secondary Immunogenicity Endpoints
  – S-268019-b was administered as an additional booster injection to participants who had received the first booster injection with S-268019-b or

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COMIRNATY and provided additional informed consent for the second booster injection with S-268019-b. After the second booster injection of S-268019-b, the GMT of SARS-CoV-2 neutralizing antibody increased from Day 365 to Days 393 and 433 in both groups regardless of infection history. For the S-268019-b group, the GMTs (95% CIs) of SARS-CoV-2 neutralizing antibody in total participants, participants without infection history, and participants with infection history were 75.23 (59.26 to 95.52), 48.54 (34.33 to 68.62), and 126.99 (100.11 to 161.09), respectively, on Day 365, 171.95 (147.04 to 201.07), 146.05 (118.03 to 180.73), and 195.55 (156.28 to 244.69), respectively, on Day 393, 161.41 (134.35 to 193.92), 106.42 (84.43 to 134.15), and 205.20 (160.70 to 262.02), respectively, on Day 433, and 100.79 (82.66 to 122.91), 56.57 (43.24 to 74.01), and 112.14 (87.17 to 144.25), respectively, on Day 547. In the S-268019-b group, the GMTs of SARS-CoV-2 neutralizing antibody after the second booster injection tended to be higher in the participants with a SARS-CoV-2 infection history before the second booster injection than in the participants without it.

- The GMTR (95% CI) of Day 393 compared with Day 29 was 1.14 (0.88 to 1.46) in the S-268019-b group and 0.77 (0.60 to 0.99) in the COMIRNATY group. The lower limit of the 95% CI for the GMTR in the S-268019-b group (0.88) was greater than the pre-specified noninferiority margin (0.67), demonstrating the noninferiority of GMT in the S-268019-b group of Day 393 to that of Day 29 (28 days after the first booster injection).
- The difference in seroresponse rates (95% CI) of SARS-CoV-2 neutralizing antibody titer (Day 393 − Day 29) was −42.1% (−57.8% to −27.9%) in the S-268019-b group and −29.7% (−45.8% to −17.5%) in the COMIRNATY group. The lower limits of the 95% CI for the seroresponse rate in the S-268019-b group (−57.8%) and the COMIRNATY group (−45.8%) were not greater than the pre-specified noninferiority margin (−10%), failing to demonstrate the noninferiority of the seroresponse rate of Day 393 to that of Day 29 in either study intervention group. The difference (95% CI) in the seroresponse rate of Day 393 in this study population compared with the seroconversion rate of Day 57 in the external control population was −33.1% (−46.1% to −20.1%) in the S-268019-b group and −20.7% (−33.7% to

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−7.7%) in the COMIRNATY group. The lower limits of the 95% CI for the difference in the S-268019-b group (−46.1%) and the COMIRNATY group (−33.7%) were not greater than the pre-specified noninferiority margin (−10%), failing to demonstrate the noninferiority of the seroresponse rate of Day 393 in this study population to the seroconversion rate of Day 57 in the external control population in either study intervention group.
A post-hoc analysis of the GMT of SARS-CoV-2 neutralizing antibody showed that there was a difference in the GMT of Day 365 between the participants with a positive seroresponse and those with a negative seroresponse of Day 393 in both groups, which might have negatively impacted the outcome of noninferiority evaluation. The GMT of SARS-CoV-2 neutralizing antibody nevertheless increased after the second booster injection in participants with a negative seroresponse on Day 393 in both groups, indicating that the immune response was indeed induced by the second booster injection with S-268019-b.

– After the second booster injection of S-268019-b, the GMT of anti-spike protein IgG antibody increased from Day 365 to Days 393, 433, and 547 in both groups regardless of infection history.
For the S-268019-b group, the GMTs (95% CIs) of anti-spike protein IgG antibody in total participants, participants without infection history, and participants with infection history were 28945.9 (22361.8 to 37468.6), 16566.1 (11766.0 to 23324.5), and 56374.1 (43045.2 to 73830.3), respectively, on Day 365, 49835.8 (41353.7 to 60057.7), 37549.0 (28558.5 to 49369.8), and 63728.3 (50556.9 to 80331.1), respectively, on Day 393, 48574.3 (40016.4 to 58962.6), 33368.7 (25565.7 to 43553.3), and 56961.6 (43898.4 to 73912.2), respectively, on Day 433, and 70271.2 (57882.7 to 85311.3), 43053.9 (30884.0 to 60019.3), and 73054.1 (57725.5 to 92452.9), respectively, on Day 547. In the S-268019-b group, the GMTs of anti-spike protein IgG antibody after the second booster injection were higher in the participants with a SARS-CoV-2 infection history before the second booster injection than in the participants without it.

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Efficacy:

- The demographics and baseline characteristics of the mITT population were identical to those of the immunogenicity subset.
- The number of symptomatic COVID-19 participants confirmed 14 days or later after the first booster injection was 42 of 101 participants in the S-268019-b group and 34 of 102 participants in the COMIRNATY group. The number of asymptomatic COVID-19 participants confirmed 14 days or later after the first booster injection was 4 of 101 participants in the S-268019-b group and 8 of 102 participants in the COMIRNATY group.
- The number of symptomatic COVID-19 participants confirmed after the first booster injection was 42 of 101 participants in the S-268019-b group and 34 of 102 participants in the COMIRNATY group. The number of asymptomatic COVID-19 participants confirmed after the first booster injection was 4 of 101 participants in the S-268019-b group and 8 of 102 participants in the COMIRNATY group.
- The most common variant of SARS-CoV-2 in the participants with symptomatic COVID-19 was BA.5.2.1.

Safety:

Adverse Events Reported Before the Second Booster Injection in Participants who Received the First Booster Injection on Day 1:

- No deaths or AESIs were reported in the S-268019-b group. One participant in the COMIRNATY group died from myocardial ischaemia. The myocardial ischaemia was considered unrelated to the study intervention. One nonfatal SAE was reported in 1.0% (1 of 101) of the participants in the S-268019-b group and 2 nonfatal SAEs were reported in 1.9% (2 of 103) of the participants in the COMIRNATY group. All nonfatal SAEs were considered unrelated to the study intervention.
- A total of 43 MAAEs were reported in 34.7% (35 of 101) of the participants in the S-268019-b group and 60 MAAEs were reported in 32.0% (33 of 103) of the participants in the COMIRNATY group. Most of the MAAEs in either group were considered unrelated to the study intervention.
- A total of 426 AEs were reported in 98.0% (99 of 101) of the participants in the S-268019-b group and 538 AEs were reported in 100.0% (103 of 103) of the participants in the COMIRNATY group. A total of 365 treatment-related AEs were reported in 96.0% (97 of 101) of the participants in the S-268019-b

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group and 467 treatment-related AEs were reported in 98.1% (101 of 103) of the participants in the COMIRNATY group. No substantial differences were observed in the overall incidence of AEs or treatment-related AEs between the study intervention groups. Most of the AEs in either group were considered related to the study intervention. Most of the AEs in either group were solicited AEs except for AEs related to laboratory test values.

- No apparent trends related to the study intervention were found in clinical laboratory tests, vital signs, or ECG parameters in any of the study intervention groups.

Solicited systemic AEs:

- A total of 169 solicited systemic AEs were reported in 69.3% (70 of 101) of the participants in the S-268019-b group and 240 solicited systemic AEs were reported in 79.6% (82 of 103) of the participants in the COMIRNATY group. All solicited systemic AEs were considered related to the study intervention. The overall incidence of solicited systemic AEs in the S-268019-b group was lower than that in the COMIRNATY group.
- The solicited systemic AEs with an incidence of 10% or greater in any of the groups were fatigue (42.6% in the S-268019-b group and 54.4% in the COMIRNATY group; in the same order hereinafter), myalgia (39.6% and 48.5%), fever (38.6% and 59.2%), headache (25.7% and 41.7%), and arthralgia (7.9% and 11.7%). No solicited systemic AEs were reported with a higher incidence in the S-268019-b group than in the COMIRNATY group except for nausea/vomiting (5.0% and 4.9%).
- None of the participants experienced Grade 4 or Grade 5 solicited systemic AEs. Most of the solicited systemic AEs were Grade 1 or Grade 2 in severity. Most of the solicited systemic AEs were resolved (considered "recovering/resolving" or "recovered/resolved") within 5 days. No substantial differences were observed in the duration of solicited systemic AEs between the study intervention groups. Most of the solicited systemic AEs occurred within 2 days after the first booster injection. No substantial differences were observed in the timing of onset of solicited systemic AEs between the study intervention groups.

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Solicited local AEs

- A total of 74 solicited local AEs were reported in 67.3% (68 of 101) of the participants in the S-268019-b group and 87 solicited local AEs were reported in 72.8% (75 of 103) of the participants in the COMIRNATY group. All solicited local AEs were considered related to the study intervention. The overall incidence of solicited local AEs in the S-268019-b group was slightly lower than that in the COMIRNATY group.
- The most common solicited local AE in both groups was pain (65.3% in the S-268019-b group and 72.8% in the COMIRNATY group; in the same order hereinafter), followed by erythema/redness (5.9% and 9.7%), and swelling (1.0% and 1.0%). No solicited local AEs were reported with a higher incidence in the S-268019-b group than in the COMIRNATY group. More than half of the participants in both groups experienced pain after the first booster injection.
- None of the participants experienced Grade 3, Grade 4, or Grade 5 solicited local AEs. Most of the solicited local AEs were resolved (considered "recovering/resolving" or "recovered/resolved") within 5 days. No substantial differences were observed in the duration of solicited local AEs between the study intervention groups. Most of the solicited local AEs occurred within 2 days after the first booster injection. No substantial differences were observed in the timing of onset of solicited local AEs between the study intervention groups.

Unsolicited AEs

- A total of 183 unsolicited AEs were reported in 94.1% (95 of 101) of the participants in the S-268019-b group and 211 unsolicited AEs were reported in 93.2% (96 of 103) of the participants in the COMIRNATY group. A total of 122 treatment-related unsolicited AEs were reported in 82.2% (83 of 101) of the participants in the S-268019-b group and 140 treatment-related unsolicited AEs were reported in 83.5% (86 of 103) of the participants in the COMIRNATY group. No substantial differences were observed in the overall incidence of unsolicited AEs between the study intervention groups. Most of the unsolicited AEs in either group were considered related to the study intervention.

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- The unsolicited AEs with an incidence of 10% or greater in any of the groups were neutrophil percentage increased (76.2% in the S-268019-b group and 78.6% in the COMIRNATY group; in the same order hereinafter), C-reactive protein increased (32.7% and 44.7%), nasopharyngitis (16.8% and 13.6%), and white blood cell count increased (8.9% and 10.7%). All unsolicited AEs with an incidence of 10% or greater, except for nasopharyngitis (16.8% and 13.6%), were considered related to the study intervention. None of the unsolicited AEs reported in the S-268019-b group occurred with an incidence by 10% or greater than those in the COMIRNATY group. More than half of the participants in both groups experienced neutrophil percentage increased after the first booster injection.

Adverse Events Reported After the Second Booster Injection in Participants who Received the Second Booster Injection on Day 365 (ie, 4 Injections of SARS-CoV-2 Vaccine in Total):

- No deaths, nonfatal SAEs, or AESIs were reported in the S-268019-b group. One nonfatal SAE was reported in 1.2% (1 of 83) of the participants in the COMIRNATY group. The nonfatal SAE was considered unrelated to the study intervention.
- A total of 14 MAAEs were reported in 17.1% (14 of 82) of the participants in the S-268019-b group and 29 MAAEs were reported in 24.1% (20 of 83) of the participants in the COMIRNATY group. Most of the MAAEs in either group were considered unrelated to the study intervention.
- A total of 201 AEs were reported in 82.9% (68 of 82) of the participants in the S-268019-b group and 206 AEs were reported in 81.9% (68 of 83) of the participants in the COMIRNATY group. A total of 178 treatment-related AEs were reported in 79.3% (65 of 82) of the participants in the S-268019-b group and 176 treatment-related AEs were reported in 74.7% (62 of 83) of the participants in the COMIRNATY group. No substantial differences were observed in the overall incidence of AEs or treatment-related AEs between the study intervention groups. Most of the AEs in either group were considered related to the study intervention. Most of the AEs in either group were solicited AEs except for AEs related to laboratory test values.

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- No apparent trends related to the study intervention were found in clinical laboratory tests, vital signs, or ECG parameters in any of the study intervention groups.

Solicited systemic AEs:

- The overall incidence of solicited systemic AEs which occurred after the second booster injection with S-268019-b was 53.7% (44 of 82) in the S-268019-b group and 44.6% (37 of 83) in the COMIRNATY group. All solicited systemic AEs were considered related to the study intervention. The overall incidence of solicited systemic AEs in the S-268019-b group was slightly higher than that in the COMIRNATY group.
- The solicited systemic AEs with an incidence of 10% or greater in any of the groups were fatigue (41.5% in the S-268019-b group and 39.8% in the COMIRNATY group; in the same order hereinafter), fever (36.6% and 27.7%), headache (22.0% and 25.3%), and myalgia (22.0% and 21.7%). The incidence of fever in the S-268019-b group was slightly higher than that in the COMIRNATY group. The incidence of remaining solicited systemic AEs was comparable between the study intervention groups.
- None of the participants experienced Grade 4 or Grade 5 solicited systemic AEs. Most of the reported solicited systemic AEs were Grade 1 or Grade 2 in severity. Most of the solicited systemic AEs were resolved (considered "recovering/resolving" or "recovered/resolved") within 4 days. No substantial differences were observed in the duration of solicited systemic AEs between the study intervention groups. Most of the solicited systemic AEs occurred within 2 days after the second booster injection with S-268019-b. No substantial differences were observed in the timing of onset of solicited systemic AEs between the study intervention groups.

Solicited local AEs

- The overall incidence of solicited local AEs which occurred after the second booster injection with S-268019-b was 68.3% (56 of 82) in the S-268019-b group and 66.3% (55 of 83) in the COMIRNATY group. All solicited local AEs were considered related to the study intervention. No substantial differences were observed in the overall incidence of solicited local AEs between the study intervention groups.

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- The most common solicited local AE in both groups was pain (65.9% in the S-268019-b group and 66.3% in the COMIRNATY group; in the same order hereinafter), followed by erythema/redness (24.4% and 20.5%), and swelling (0% and 1.2%). The incidence of solicited local AEs was comparable between the study intervention groups.
- None of the participants experienced Grade 4 or Grade 5 solicited local AEs. All of the reported solicited local AEs were Grade 1 or Grade 2 in severity except for Grade 3 erythema/redness (1.2% and 0%). Most of the solicited local AEs were resolved (considered "recovering/resolving" or "recovered/resolved") within 4 days. No substantial differences were observed in the duration of solicited local AEs between the study intervention groups. Most of the solicited local AEs occurred within 2 days after the second booster injection with S-268019-b. No substantial differences were observed in the timing of onset of solicited local AEs between the study intervention groups.

Unsolicited AEs

- The overall incidence of unsolicited AEs which occurred after the second booster injection with S-268019-b was 22.0% (18 of 82) in the S-268019-b group and 27.7% (23 of 83) in the COMIRNATY group. The overall incidence of treatment-related unsolicited AEs which occurred after the second booster injection with S-268019-b was 1.2% (1 of 82) in the S-268019-b group and 3.6% (3 of 83) in the COMIRNATY group. The overall incidence of unsolicited AEs in the S-268019-b group was slightly lower than that in the COMIRNATY group. Most of the unsolicited AEs in either group were considered unrelated to the study intervention.
- The most common unsolicited AE in both groups was SARS-CoV-2 antibody test positive (6.1% in the S-268019-b group and 3.6% in the COMIRNATY group) and all of the events were considered unrelated to the study intervention.

CONCLUSIONS

This study was a phase 2/3, single-center, randomized, observer-blinded, active-controlled study to evaluate noninferiority in immunogenicity of S-268019-b (recombinant protein vaccine) compared to COMIRNATY (mRNA vaccine) and to assess safety of S-268019-b. The study enrolled a total of 206 participants (S-268019-b group: 102 participants; COMIRNATY group: 104 participants) aged 21

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years or older who had completed 2 injections of COMIRNATY given as primary vaccination at least 6 months before enrollment.

The primary objective of this study was to evaluate the noninferiority in immunogenicity of S-268019-b given as the first booster injection compared to COMIRNATY in participants who had completed vaccination with 2 injections of COMIRNATY. The results verified that S-268019-b was noninferior to COMIRNATY in immunogenicity in terms of GMTR and seroresponse rate of SARS-CoV-2 neutralizing antibody on Day 29 (28 days after the first booster injection). The secondary endpoint evaluations also showed favorable immunogenicity of S-268019-b.

An additional booster injection with S-268019-b was administered to participants who had received the first booster injection in this study and provided additional informed consent for the second booster injection. The immune response was induced by the second booster injection with S-268019-b: the GMT of SARS-CoV-2 neutralizing antibody of Day 393 (28 days after the second booster injection) was higher than that of Day 29 (28 days after the first booster injection) of this study and Day 57 (28 days after the second injection of primary vaccination) of the external control population of Study 2025U0231.

The number of symptomatic COVID-19 participants confirmed 14 days or later after the first booster injection was 42 of 101 participants in the S-268019-b group and 34 of 102 participants in the COMIRNATY group. The number of asymptomatic COVID-19 participants confirmed 14 days or later after the first booster injection was 4 of 101 participants in the S-268019-b group and 8 of 102 participants in the COMIRNATY group. The most common variant of SARS-CoV-2 in the participants with symptomatic COVID-19 was BA.5.2.1.

There were no significant findings of safety or tolerability of concern up to Day 547 (28 days after the first booster injection or 182 days after the second booster injection) in participants who had completed vaccination with 2 injections of COMIRNATY and received 2 injections of the study intervention in this study, ie, the first booster injection with S-268019-b or COMIRNATY and the second booster injection with S-268019-b. Most of AEs were those expected to occur after vaccination.

There were no COVID-19 impacts in this study.

Sponsor: Shionogi & Co., Ltd.	**Individual Study Table** **Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable.	**Volume:**	
Name of Active Ingredient: S-268019	**Page:**	
In conclusion, the booster vaccination with S-268019-b, ie, maximum 2 additional booster injections, boosted immunity against SARS-CoV-2 and was generally safe and well-tolerated in participants who had completed primary vaccination.		
Date of Report: 21 Feb 2024		