2. SYNOPSIS

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Study Title:
A Phase 3, Open-label Study to Evaluate Safety of a Booster Dose of S-268019 in Adults and Older Adults Who Have Completed COVID-19 Vaccine as a Primary Series

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

Publication (reference): Not applicable

Studied Period: 31 Mar 2023 (the date of the last participant last visits)

Phase of Development: Phase 3

Objectives and Endpoints:

Objectives	Endpoints
Primary	
● To assess the safety of S-268019-b as a booster vaccination in adults (aged between 20 and 64 years) and older adults (aged at least 65 years) who have completed 2 injections of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine as a primary vaccination.	● The incidence of adverse events (AEs)/treatment-related AEs/serious AEs (SAEs)/solicited AEs/medically-attended AEs (MAAEs)/AEs of special interest (AESIs), vital signs, laboratory test values, and electrocardiograms (ECGs)
Secondary	
● To assess the immunogenicity of S-268019-b as a booster vaccination in adults (aged between 20 and 64 years) and older adults (aged at least 65 years) who have completed 2 injections of SARS-CoV-2 vaccine as a primary vaccination.	● The following items for SARS-CoV-2 neutralizing antibody titer and anti-spike protein immunoglobulin G (IgG) antibody titer – Geometric mean titer (GMT) – Geometric mean fold rise (GMFR) – Seroresponse rate – Seroprotection rate

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● To investigate the clinical efficacy of S-268019-b as a booster vaccination in adults (aged between 20 and 64 years) and older adults (aged at least 65 years) who have completed 2 injections of SARS-CoV-2 vaccine as a primary vaccination.	● The number of participants with symptomatic coronavirus disease 2019 (COVID-19) or asymptomatic COVID-19 14 days or later after vaccination of S-268019-b ● The number of participants with symptomatic COVID-19 or asymptomatic COVID-19 after vaccination of S-268019-b
● To assess the immunogenicity of S-268019-b as second booster vaccination in adults aged between 20 and 64 years and older adults aged at least 65 years who have received S-268019-b as first booster vaccination.	● The GMT and seroresponse rate for SARS-CoV-2 neutralizing antibody titer and the GMT for anti-spike protein IgG antibody
● To assess the safety of S-268019-b as second booster vaccination in adults aged between 20 and 64 years and older adults aged at least 65 years who have received S-268019-b as first booster vaccination.	● 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

Methodology:

This study was a Phase 3, single-center, non-controlled, open-label study to evaluate safety and immunogenicity of S-268019-b as a booster vaccination in adults (aged between 20 and 64 years) and older adults (aged at least 65 years) who had completed 2 injections of SARS-CoV-2 vaccine as a primary vaccination. This study consisted of 3 cohorts (A to C). Cohort A consisted of adults who had completed 2 injections of SPIKEVAX as a primary vaccination. Cohort B consisted of older adults who had completed 2 injections of COMIRNATY as a primary vaccination. Cohort C

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consisted of older adults who had completed 2 injections of SPIKEVAX as a primary vaccination. Participants received the first booster injection with of S-268019-b via intramuscular injection on Day 1, and have been monitored for approximately 12 months. Furthermore, participants who provided additional informed consent for the second booster vaccination received 1 injection of S-268019-b via intramuscular injection on Day 151, and have been monitored for approximately 12 months after the first booster injection.

Number of Participants (Planned and Analyzed):

Planned: 100 for Cohort A (adults [aged between 20 and 64 years]) and 25 each for Cohorts B and C (older adults [aged at least 65 years])

Registered: 103 for Cohort A, 29 for Cohort B, and 23 for Cohort C

Analyzed for immunogenicity:

- Immunogenicity subset: 150 (100 in Cohort A, 29 in Cohort B, and 21 in Cohort C)
- Immunogenicity subset for second booster vaccination: 82 (49 in Cohort A, 18 in Cohort B, and 15 in Cohort C)

Analyzed for efficacy:

- Modified intent-to-treat (mITT) population: 150 (100 in Cohort A, 29 in Cohort B, and 21 in Cohort C)

Analyzed for safety:

- Safety analysis population: 155 (103 in Cohort A, 29 in Cohort B, and 23 in Cohort C)
- Safety analysis population for second booster vaccination: 86 (51 in Cohort A, 18 in Cohort B, and 17 in Cohort C)

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria
   - Male and female adults (aged between 20 and 64 years) and older adults (aged at least 65 years) at the time of signing the informed consent form (ICF).
   - At least 6 months and not greater than 8 months have passed after completion of the second injection with approved SARS-CoV-2 vaccines (adults: SPIKEVAX only, older adults: COMIRNATY or SPIKEVAX).
2. Exclusion criteria
   - Tested positive for SARS-CoV-2 infection (as determined by a SARS-CoV-2 antigen test) at screening.

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- Determined in the interview prior to the study intervention to have a history of SARS-CoV-2 infection.
- Participant had a contraindication to intramuscular injections or blood draws.
- Previous approved or investigational SARS-CoV-2 vaccination other than 2 injections of approved SARS-CoV-2 vaccines (adults, SPIKEVAX only; older adults, COMIRNATY or SPIKEVAX).
- 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 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 and S-268019 oil in water emulsion for injection were mixed in a ratio of 1:1 (0.25 mL each). One dose (0.5 mL mixture) of S-268019 was given in the upper arm as an intramuscular injection.

3. Packaging Lot Number
   - S-268019 injectable 40 µg/mL: [redacted]
   - S-268019 oil in water emulsion for injection 1 mL: [redacted]
   - S-268019 oil in water emulsion for injection 0.9 mL: [redacted]

Duration of Treatment:

Up to 2 days (A single injection of the assigned study intervention was administered on Day 1 in the evaluation period. In addition to Day 1, 1 injection of study intervention was administered on Day 151, if applicable.)

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

No placebo was used in this study.

Criteria for Evaluation:

Immunogenicity Assessment:

Not applicable.

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Efficacy Assessment:

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

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 a positive test result of RT-PCR and 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 partial pressure of arterial oxygen[PaO_2]/fraction of inspired oxygen [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

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

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Safety Assessment:

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

The following AEs were collected as solicited AEs (solicited systemic AEs and solicited local AEs) 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. The severity of each solicited systemic AE and pain was assessed and the longest diameter was measured for erythema/redness, induration, and swelling.

- 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, hospital, emergency room [ER], home, etc.) because of the AE. MAAEs could be serious or non-serious.

Potential immune-mediated diseases were collected as AESIs of S-268019-b. AESI could be serious or non-serious.

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The investigator or subinvestigator assessed the severity of solicited AEs reported during the study by referring to the Food and Drug Administration (FDA) guidance. If the participant died due to a solicited AE, this event was to be of Grade 5 severity.

The severity of each non-solicited AE and SAE was assessed and classified into 1 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 were performed for the immunogenicity subset.

Immunogenicity endpoint for first booster vaccination:

- GMT of SARS-CoV-2 neutralizing antibody at each time point
  For SARS-CoV-2 neutralizing antibody titer at each time point, the GMT and the corresponding 95% confidence interval (CI) were calculated by back transformation of the arithmetic mean and its 95% CI of the log-transformed titers. The 95% CI in log-transformed titer was constructed using Student's t distribution.
- GMFR of SARS-CoV-2 neutralizing antibody titer, GMT of anti-spike protein IgG antibody, and GMFR of anti-spike protein IgG antibody titer at each time point were analyzed in the same manner as the GMT of SARS-CoV-2 neutralizing antibody.
- Seroresponse rate of SARS-CoV-2 neutralizing antibody titer
  The proportion of participants with a ≥ 4-fold rise from baseline of SARS-CoV-2 neutralizing antibody titer (seroresponse) and its 95% CI were calculated at each time point. The 95% CI for antibody seroresponse rate was calculated using the Clopper-Pearson method.
- Seroprotection rate of SARS-CoV-2 neutralizing antibody titer
  The proportion of participants with a SARS-CoV-2 neutralizing antibody titer of ≥ 20 and the 95% CI were calculated at each time point. The 95% CI for seroprotection rate was calculated using the Clopper-Pearson method. The same analysis was conducted for the proportion of participants with a SARS-CoV-2 neutralizing antibody titer of ≥ 10.
- Seroresponse rate for anti-spike protein IgG antibody titer at each time point
  The proportion of participants with a ≥ 4-fold rise from baseline of anti-spike protein IgG antibody titer (seroresponse) and its 95% CI were calculated at

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each time point. The 95% CI for antibody seroresponse rate was calculated using the Clopper-Pearson method.

- Seroprotection rate for anti-spike protein IgG antibody titer at each time point
  The proportion of participants with an anti-spike protein IgG antibody titer of ≥ 3200 and the 95% CI were calculated at each time point. The 95% CI for seroprotection rate was calculated using the Clopper-Pearson method. The same analysis was conducted for the proportion of participants with an anti-spike protein IgG antibody titer of ≥ 6400.

Immunogenicity endpoint for second booster vaccination:

- GMT of SARS-CoV-2 neutralizing antibody at each time point
  For SARS-CoV-2 neutralizing antibody titer of immunogenicity subset for second booster vaccination 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.
- GMT of SARS-CoV-2 neutralizing antibody on Day 179
  For the participants in the immunogenicity subset for second booster vaccination, the paired-samples t-test for the non-inferiority and superiority evaluation to compare GMTs between Day 29 and 28 days after the second booster injection in this study (Day 179) was performed, and the geometric mean titer ratio (GMTR) and the corresponding 95% CI were calculated. The non-inferiority was to be confirmed if the lower limit of the 95% CI for the GMTR was greater than 0.67 and the superiority was to be confirmed if the lower limit of the 95% CI for the GMTR was greater than 1.0.
  In addition, the non-inferiority of the GMT on 28 days after the second booster injection in this study (Day 179) compared to the GMT of 28 days after the second injection of primary vaccination (Day 57) of the external control population was evaluated. Participants in Cohort A were compared to adults (aged between 20 and 64 years old) of the external control population. Participants in Cohort B, Cohort C, and the merged cohort (B + C) were compared to older adults (aged at least 65 years old) of the external control population. The GMTR and the corresponding 95% CI were estimated by back transformation of the intervention mean difference of the log-transformed titers (the arithmetic mean on Day 179 of participants in the immunogenicity subset for second booster vaccination − the arithmetic mean on Day 57 of participants of the external control population) and its 95% CI as the non-inferiority and superiority evaluation. The non-inferiority was to be confirmed

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if the lower limit of the 95% CI for the GMTR was greater than 0.67 and the superiority was to be confirmed if the lower limit of the 95% CI for the GMTR was greater than 1.0.

- Seroresponse rate for SARS-CoV-2 neutralizing antibody titer on Day 179
  For the participants in the immunogenicity subset for second booster vaccination, 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 that on 28 days after the second booster injection (Day 179) for SARS-CoV-2 neutralizing antibody titer. The non-inferiority was to be confirmed if the lower limit of the 95% CI for the difference between the seroresponse rate was greater than −10%.
  In addition, the non-inferiority of the seroresponse rate on 28 days after the second booster injection (Day 179) 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. Participants in Cohort A were compared to adults (aged between 20 and 64 years old) of the external control population. Participants in Cohort B, Cohort C and the merged cohort (B + C) were compared to older adults (aged at least 65 years old) of the external control population. The difference between the seroresponse rate on Day 179 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 non-inferiority evaluation. The non-inferiority was to be confirmed if the lower limit of the 95% CI for the difference between the rate was greater than −10%.
- GMT of anti-spike protein IgG antibody at each time point
  For anti-spike protein IgG antibody titer of immunogenicity subset for second booster vaccination 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.

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 were tabulated. The number of participants in the mITT population with symptomatic COVID-19 or asymptomatic COVID-19 confirmed after the study intervention were also tabulated.

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Safety Analyses:

Adverse events were coded and classified by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA), Version 24.1. Of the AEs reported in the electronic case report form (eCRF), TEAEs that occurred after the study intervention were used for the safety analysis. The number and proportion of participants who experienced AEs were summarized by SOC and PT. For these summaries, participants with multiple AEs were counted only once within an SOC and PT. Treatment-related AEs, MAAEs, treatment-related MAAEs, AESIs, and treatment-related AESIs were summarized in the same manner. The number and proportion of participants with TEAEs and its 95% CI were summarized. 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 TEAE leading to death, other serious TEAEs, MAAEs, and AESIs were similarly summarized. These data were also summarized by severity, duration, outcome, and timing of onset. Treatment-related AEs were summarized in the same manner. The number and proportion of participants who experienced solicited systemic AEs were summarized by the AE name (fever, nausea/vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, and chills). The number and proportion of participants with solicited systemic AEs and its 95% CI were summarized. The 95% CI for the incidence was calculated using the Clopper-Pearson method. These data were also summarized by severity, duration, and timing of onset. Solicited local AEs, treatment-related solicited systemic AEs, and treatment-related solicited local AEs were summarized in the same manner. The number and proportion of participants who experienced unsolicited AEs were summarized by SOC and PT. The number and proportion of participants with unsolicited AEs and its 95% CI were summarized. The 95% CI for the incidence was calculated using the Clopper-Pearson method.

Summary statistics for vital signs, laboratory test results, and measurements on 12-lead ECG and change from baseline at each scheduled time point were presented. The baseline was the last measurement obtained immediately prior to study intervention.

Summary of Results:

Demographics and Other Baseline Characteristics:

- In the immunogenicity subset, all participants were Asian, and the proportions of male participants were 50.0%, 75.9%, and 66.7% in Cohort A, Cohort B, and Cohort C, respectively (hereinafter the same order). The median age (min-max) was 48.0 (20-64) years, 67.0 (65-75) years and 67.0 (65-79) years, respectively. The mean body mass index (BMI) (standard deviation [SD]) was

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23.06 (3.50) kg/m^2, 23.09 (3.85) kg/m^2, and 25.61 (3.23) kg/m^2, respectively. No participants had previous SARS-CoV-2 infection or positive for anti-SARS-CoV-2 N-protein antibody test at screening. The time from the second injection of SARS-CoV-2 vaccine given as a primary vaccination in 60.0% in Cohort A was 6 months or more and less than 7 months, but the majority of participants in Cohorts B and C were 7 months or more and less than 8 months (62.1% in Cohort B and 81.0% in Cohort C).

- In the immunogenicity subset for second booster vaccination, all participants were Asian, and the proportions of male participants were 55.1%, 77.8%, and 73.3% in Cohort A, Cohort B, and Cohort C, respectively (hereinafter the same order). The median age (min-max) was 50.0 (22-64) years, 67.5 (65-75) years and 67.0 (65-74) years, respectively. The mean BMI (SD) was 23.43 (3.97) kg/m^2, 23.65 (4.21) kg/m^2, and 26.39 (2.86) kg/m^2, respectively.
- For the external control population, all participants were Asian, and the proportions of male participants were 65.9% and 79.2% in the < 65 years group and the ≥ 65 years group, respectively. The median age (min-max) was 44.0 (20-64) years and 68.5 (65-86) years, respectively. The mean BMI (SD) was 23.59 (4.36) kg/m^2 and 23.37 (2.65) kg/m^2, respectively.
- There were no significant differences in demographics and characteristics between the participants in Cohort A and the < 65 years group of the external control population, or participants in Cohort B or C and the ≥ 65 years group of the external control population.

Immunogenicity:

- First Booster Vaccination Without Additional Injection on Day 151
  - The GMT (95% CI) of SARS-CoV-2 neutralizing antibody at baseline was 12.14 (10.53, 14.00), 3.41 (2.93, 3.97), and 10.34 (6.13, 17.44) in Cohort A, Cohort B, and Cohort C, respectively. The GMTs of SARS-CoV-2 neutralizing antibody in all cohorts increased from baseline to Day 29 after the first booster injection. The GMT (95% CI) on Day 29 was 99.35 (83.44, 118.29), 76.14 (55.38, 104.67), and 129.96 (88.79, 190.22) in Cohort A, Cohort B, and Cohort C, respectively.
  - The GMFR (95% CI) of SARS-CoV-2 neutralizing antibody titer on Day 29 was 8.06 (6.54, 9.92), 22.07 (16.12, 30.23), and 11.71 (7.45, 18.41) in Cohort A, Cohort B, and Cohort C, respectively.

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- The seroresponse rate (95% CI) of SARS-CoV-2 neutralizing antibody titer on Day 29 was 86.5% (78.0%, 92.6%), 100.0% (87.7%, 100.0%), and 95.0% (75.1%, 99.9%) in Cohort A, Cohort B, and Cohort C, respectively.
- The seroprotection rate (95% CI) of SARS-CoV-2 neutralizing antibody titer (20 or higher) on Day 29 was 99.0% (94.3%, 100.0%), 100.0% (87.7%, 100.0%), and 100.0% (83.2%, 100.0%) in Cohort A, Cohort B, and Cohort C, respectively.
- The GMT (95% CI) of anti-spike protein IgG antibody at baseline was 2039.3 (1763.2, 2358.6), 508.0 (389.3, 663.0), and 1766.5 (937.8, 3327.8) in Cohort A, Cohort B, and Cohort C, respectively. The GMTs of anti-spike protein IgG antibody in all cohorts increased from baseline to Day 29 after the first booster injection. The GMT (95% CI) on Day 29 was 34171.9 (28792.1, 40556.9), 21000.6 (14917.8, 29563.6), and 49455.9 (32689.2, 74822.5) in Cohort A, Cohort B, and Cohort C, respectively.
- The GMFR (95% CI) of anti-spike protein IgG antibody titer on Day 29 was 16.83 (13.71, 20.66), 39.99 (28.36, 56.38), and 25.99 (15.03, 44.96) in Cohort A, Cohort B, and Cohort C, respectively.
- The seroresponse rate (95% CI) of anti-spike protein IgG antibody titer on Day 29 was 97.9% (92.7%, 99.7%), 100.0% (87.7%, 100.0%), and 95.0% (75.1%, 99.9%) in Cohort A, Cohort B, and Cohort C, respectively.
- The seroprotection rate (95% CI) of anti-spike protein IgG antibody titer (6400 or higher) on Day 29 was 100.0% (96.2%, 100.0%), 96.4% (81.7%, 99.9%), and 100.0% (83.2%, 100.0%) in Cohort A, Cohort B, and Cohort C, respectively.
- After Day 29, although the number of participants was limited, all immunogenicity endpoints for the first booster injection gradually declined until Day 365 in participants who did not receive second injection of study intervention.
- The interferon γ (IFN-γ)-producing cells that respond to the first booster injection with S-268019-b increased after the first booster injection in all cohorts.
- The first booster injection with S-268019-b 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 the first booster injection in all cohorts.

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- Second Booster Vaccination (a Total 4 Injections of SARS-CoV-2 Vaccine) on Day 151
  - The GMTs of SARS-CoV-2 neutralizing antibody increased by the second booster injection with S-268019-b in all cohorts and the GMTs on Day 179 (28 days after the second booster injection) demonstrated non-inferiority compared to that on Day 29 (28 days after the first booster injection) in this study or to the GMTs of 28 days after the second injection of primary vaccination of the external control population (Study 2025U0231). The GMTs then gradually declined until Day 365.
  - Meanwhile, non-inferiority for the seroresponse rate of SARS-CoV-2 neutralizing antibody titer on Day 179 compared to that on Day 29 (28 days after the first booster injection) in this study or the seroconversion rate on Day 57 (28 days after the second injection of primary vaccination) of the external control population (Study 2025U0231) was not demonstrated. The post-hoc analysis of GMTs of SARS-CoV-2 neutralizing antibody by positive or negative seroresponse on Day 179 revealed that the GMT of SARS-CoV-2 neutralizing antibody on Day 151 (before the second booster injection) in participants with a negative seroresponse on Day 179 was higher than that in participants with a positive seroresponse on Day 179 in all cohorts, suggesting that the differences between the GMTs of SARS-CoV-2 neutralizing antibody on Day 151 (before the second booster injection) made it difficult to demonstrate the non-inferiority about the seroresponse rate on Day 179. The GMT in participants with a negative seroresponse on Day 179 nevertheless increased by the second booster injection, indicating that the immune response was also induced by the second booster injection with S-268019-b in participants with a negative seroresponse on Day 179. To reduce the GMT differences between participants with a positive seroresponse on Day 179 and participants with a negative seroresponse on Day 179, the seroresponse rate on Day 179 was calculated as a post-hoc analysis using an alternative baseline, SARS-CoV-2 neutralizing antibody titer on Day 1 (before the first booster injection), instead of SARS-CoV-2 neutralizing antibody titer on Day 151 (before the second booster injection). The post-hoc analysis suggested that the seroresponse rate on Day 179 was comparable with that on Day 29 in this study or with the

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seroconversion rate on Day 57 of the external control population (Study 2025U0231) in all cohorts.

- After the second booster injection with S-268019-b, the GMTs of anti-spike protein IgG antibody in all cohorts stayed steady from Day 151 to Day 179, then gradually increased to Day 271, after that decreased to Day 365.
- The IFN-γ-producing cells that respond to the second booster injection with S-268019-b were present even approximately 4 months (on Day 271) after the second booster injection.
- The second booster injection with S-268019-b induced a higher percentage of Th1 cells (which produce IFN-γ or IL-2) than that of Th2 cells (which produce IL-4 or IL-5) after the second booster injection in all cohorts.

Clinical Efficacy:

- The number of participants with symptomatic COVID-19 14 days or later after the first study intervention was 10, 1, and 3 participants in Cohort A, Cohort B, and Cohort C, respectively. The number of participants with asymptomatic COVID-19 14 days or later after the first study intervention was 16, 3, and 0 participants in Cohort A, Cohort B, and Cohort C, respectively.

Safety:

- Safety of Single Booster Vaccination (Without Additional Injection on Day 151)
  - No deaths were reported. An SAE of Grade 3 pancreatic carcinoma was reported in 1 participant (4.3%) of Cohort C but the event was not treatment-related.
  - A total of 537 treatment-related AEs were reported in 97.1% (100/103) of participants in Cohort A, 79.3% (23/29) of participants in Cohort B, and 87.0% (20/23) of participants in Cohort C. Most of AEs were treatment-related.
  - A total of 242 solicited systemic AEs was reported in 68.0% (70/103) of participants in Cohort A, 34.5% (10/29) of participants in Cohort B, and 56.5% (13/23) of participants in Cohort C. A total of 237 treatment-related solicited systemic AEs was reported in 68.0% (70/103) of participants in Cohort A, 34.5% (10/29) of participants in Cohort B, and 56.5% (13/23) of participants in Cohort C. Most of the solicited systemic AEs and solicited local AEs were treatment-related.

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  - Most common solicited systemic AEs (25% or greater incidence in any cohort) were fatigue (49.5%, 17.2%, and 34.8% in Cohort A, Cohort B, and Cohort C, respectively) and headache (33.0%, 24.1%, and 17.4%). Most of the solicited systemic AEs were treatment-related. No Grade 3 or above solicited systemic AEs were reported in any cohort.
  - Most common solicited local AEs (40% or greater incidence in any cohort) were pain (92.2%, 75.9%, and 78.3% in Cohort A, Cohort B, and Cohort C, respectively) and erythema/redness (44.7%, 37.9%, and 43.5%). Most of the solicited local AEs were treatment-related. The Grade 3 solicited local AEs were reported for 3 (2.9%) participants in Cohort A; swelling in 2 participants, erythema/redness and pain each in 1 participant. Grade 3 erythema/redness was reported for 1 (4.3%) participant in Cohort C. All of them were treatment-related. No Grade 4 or Grade 5 solicited local AEs were reported.
  - The median duration of the solicited systemic AEs was 2.0 days from AE onset in any cohort. The median duration of the solicited local AEs was 4.0, 4.0, and 3.5 days from the onset of AE in Cohort A, Cohort B, and Cohort C, respectively. The median timing of onset of the solicited systemic AEs was 2.0 days after study intervention in any cohort. The median timing of onset of the solicited local AEs was 1.0, 2.0, and 2.0 days after study intervention in Cohort A, Cohort B, and Cohort C, respectively.
  - MAAEs were reported in 17 (16.5%), 2 (6.9%), and 3 (13.0%) participants in Cohort A, Cohort B, and Cohort C, respectively. The MAAEs that were reported in 2 or more participants were herpes zoster (2 participants in Cohort A) and diarrhoea (each 1 participant in Cohort A and Cohort B). Other MAAEs were reported in 1 participant each in any cohort. Treatment-related MAAEs were headache, chills, and vaccination site pain reported in Cohort A.
  - No AESIs were reported.
  - No notable findings were reported in clinical laboratory evaluation, vital signs, or 12-lead ECGs in this study.
- Safety of Second Booster Vaccination (a Total 4 Injections of SARS-CoV-2 Vaccine) on Day 151

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- No deaths were reported. SAEs which occurred after the second booster injection of study intervention were reported in 1 participant each in Cohort A (loose body in joint) and in Cohort C (brain stem infarction). But both events were not treatment-related. No SAEs were reported in Cohort B.
- A total of 366 AEs which occurred after the second booster injection of study intervention were reported in 94.1% (48/51)of participants in Cohort A, 83.3% (15/18) of participants in Cohort B, and 94.1% (16/17) of participants in Cohort C. Most of them were treatment-related.
- Solicited systemic AEs which occurred after the second booster injection of study intervention were reported in 68.6% (35/51) of participants in Cohort A, 27.8% (5/18) of participants in Cohort B, and 47.1% (8/17) of participants in Cohort C. The incidence of treatment-related solicited systemic AEs was the same as that of solicited systemic AEs in each cohort.
- Solicited local AEs which occurred after the second booster injection of study intervention were reported in 90.2% (46/51) of participants in Cohort A, 77.8% (14/18) of participants in Cohort B, and 88.2% (15/17) of participants in Cohort C. The incidence of treatment-related solicited local AEs was the same as that of solicited local AEs in each cohort.
- The median duration of the solicited systemic AEs which occurred after the second booster injection of study intervention was 2.0 days from AE onset in any cohort. The median duration of the solicited local AEs which occurred after the second booster injection of study intervention was 4.0 days from the onset of AE in any cohort. The median timing of onset of the solicited systemic AEs which occurred after the second booster injection of study intervention was 2.0 days after study intervention in any cohort. The median timing of onset of the solicited local AEs which occurred after the second booster injection of study intervention was 1.0, 2.0, and 2.0 days after study intervention in Cohort A, Cohort B, and Cohort C, respectively.
- MAAEs which occurred after the second booster injection of study intervention were reported in 9 (17.6%), 3 (16.7%), and 2 (11.8%) participants in Cohort A, Cohort B, and Cohort C, respectively.

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– No AESIs occurred after the second booster injection of study intervention.
– No notable findings were reported in clinical laboratory evaluation, vital signs, or 12-lead ECGs after the second booster injection of study intervention.

CONCLUSIONS

This study evaluated safety and immunogenicity of S-268019-b as a booster vaccination in adults (aged between 20 and 64 years) and older adults (aged at least 65 years) who had completed 2 injections of SARS-CoV-2 vaccine as a primary vaccination.

This study consisted of 3 cohorts (A to C). Cohort A consisted of adults who had completed 2 injections of SPIKEVAX as a primary vaccination. Cohort B consisted of older adults who had completed 2 injections of COMIRNATY as a primary vaccination. Cohort C consisted of older adults who had completed 2 injections of SPIKEVAX as a primary vaccination.

The GMTs of SARS-CoV-2 neutralizing antibody and anti-spike protein IgG antibody increased from baseline to Day 29 (approximately 8 to 22-fold rise and 16 to 40-fold rise, respectively) after first booster injection with S-268019-b in all cohorts. After the second booster injection with S-268019-b on Day 151, which was administered approximately 5 months after the first booster injection, the GMTs of SARS-CoV-2 neutralizing antibody increased in all cohorts with the GMTs on Day 179 (28 days after the second booster injection) demonstrating non-inferiority compared to that on Day 29 (28 days after the first booster injection) in this study or to that of 28 days after the second injection of primary vaccination of the external control population (Study 2025U0231). The GMTs then gradually declined until Day 365 (the last observation point of this study). The GMTs of anti-spike protein IgG antibody after the second booster injection with S-268019-b in all cohorts stayed steady from Day 151 to Day 179, and then gradually increased to Day 271, after that decreased to Day 365. These results suggested that both first and second injections with S-268019-b can induce a sufficient immune response as a booster vaccination in adults or older adults who had completed 2 injections of SPIKEVAX as a primary vaccination and older adults who had completed 2 injections of COMIRNATY as a primary vaccination.

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There were no significant concerns about the safety of both first and second booster injections with S-268019-b. The safety of S-268019-b was considered generally acceptable.		
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