2. SYNOPSIS

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Study Title:
An Open-Label Phase 2/3 Study of S-268019

Investigators and Study Centers: This study was a multicenter study conducted at 23 sites in Japan.

Publication (reference): Not applicable.

Studied Period:
From 20 Oct 2021 to 10 Jan 2023 (the date of the last-participant-last-visit)

Phase of Development: Phase 2/3

Objectives and Endpoints:

Objectives and Endpoints for Main Part

Objectives	Endpoints
Primary	
• To assess the safety of S-268019-b at the end of the evaluation period.	• Incidence of adverse events (AEs)/treatment-related AEs/serious AEs (SAEs)/solicited AEs/medically-attended adverse events (MAAEs)/adverse events of special interest (AESIs), vital signs, laboratory tests, and electrocardiograms (ECGs)
Secondary	
• To assess the immunogenicity after vaccination of S-268019-b.	• The following items for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) neutralizing antibody titer and anti-spike protein immunoglobulin G (IgG) antibody titer - Geometric mean titer (GMT) - Geometric mean fold rise (GMFR) - Seroconversion rate
• To assess the safety of S-268019-b at the end of the follow-up period.	• Incidence of AEs/treatment-related AEs/SAEs/solicited AEs/MAAEs/AESIs, vital signs, laboratory tests, and ECGs
• To investigate the clinical efficacy after vaccination of S-268019-b.	• The number of participants with symptomatic COVID-19 or asymptomatic COVID-19 14 days or later after the second administration of S-268019-b

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	• The number of participants with symptomatic COVID-19 or asymptomatic COVID-19 after the first administration of S-268019-b
Exploratory	
• To assess other immunological indices.	• Cellular immunity - Human leukocyte antigen (HLA)-A genotyping - Cytokine-producing cell count • Type 1 helper T cells (Th1)/Type 2 helper T cells (Th2) balance (Th1/Th2 balance) - T cell cytokine assay • Biomarkers

Objectives and Endpoints for Subpart

Objectives	Endpoints
Primary	
• To verify noninferiority of immunogenicity of the third administration of S-268019-b 28 days post-dose to that of the second administration of S-268019-b 28 days post-dose in adult participants in Cohort A who have neither history of SARS-CoV-2 infection nor history of SARS-CoV-2 vaccination and in participants in Cohort B.	• SARS-CoV-2 neutralizing antibody titer on Day 239
Secondary	
• To compare the post-vaccination immunogenicity of the third administration of S-268019-b to that of 28 days after the second administration of S-268019-b.	• The following items for SARS-CoV-2 neutralizing antibody titer and anti-spike protein IgG antibody titer other than the primary endpoint - GMT - GMFR - Seroresponse rate
• To assess the safety of S-268019-b after the third administration of S-268019-b.	• Incidence of AEs/treatment-related AEs/SAEs/solicited AEs/MAAEs/AESIs, vital signs, laboratory tests, and ECGs

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• To investigate the clinical efficacy after the third administration of S-268019-b.	• The number of participants with symptomatic COVID-19 or asymptomatic COVID-19 14 days or later after the third administration of S-268019-b • The number of participants with symptomatic COVID-19 or asymptomatic COVID-19 after the third administration of S-268019-b
Exploratory	
• To assess other immunological indices after the third administration of S-268019-b.	• Cellular immunity - HLA-A genotyping - Cytokine-producing cell count • Th1/Th2 balance - T cell cytokine assay • Biomarkers

Methodology:

This study was a multicenter, uncontrolled, open-label study, and a dose selected based on the results of a Phase 1/2 double-blind study of S-268019 (Study 2026U0221) was administered. This study consisted of 2 cohorts, Cohort A which included both adult (20 to 64 years) and elderly (65 years or older) participants, and Cohort B which included only elderly participants. Elderly participants who were determined in the interview at screening to have neither history of SARS-CoV-2 infection nor history of SARS-CoV-2 vaccination were included in Cohort B, and other elderly participants were included in Cohort A. Participants who received the third administration of study intervention on Day 211 entered Subpart for verification of noninferiority of immunogenicity after the booster vaccination compared to the primary vaccination with S-268019-b as well as for evaluation of the immunogenicity and safety and investigation of the clinical efficacy of the booster vaccination with S-268019-b.

The target number of participants enrolled in Cohort A was 3000. At least 2000 adult participants determined in the interview at screening to have neither history of SARS-CoV-2 infection nor history of SARS-CoV-2 vaccination, at least 30 adult participants determined to have a history of SARS-CoV-2 vaccination regardless of whether or not having a history of SARS-CoV-2 infection, and at least 30 adult participants determined to have a history of SARS-CoV-2 infection but not to have a

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history of SARS-CoV-2 vaccination were enrolled, and the minimum number of elderly participants was not specified.

Some participants in Cohort A corresponding to the following were categorized as Naive, Vaccination History, and Infection History, respectively:

- Naive: Adult (20 to 64 years) participants without history of SARS-CoV-2 infection or history of SARS-CoV-2 vaccination at screening and whose results of anti-SARS-CoV-2 nucleocapsid protein (N-protein) antibody test were negative at screening
- Vaccination History: Adult (20 to 64 years) participants with a history of SARS-CoV-2 vaccination regardless of a history of SARS-CoV-2 infection at screening
- Infection History: Adult (20 to 64 years) participants with a history of SARS-CoV-2 infection and without a history of SARS-CoV-2 vaccination at screening

The target number of participants enrolled in Cohort B was 100 (elderly participants determined in the interview at screening to have neither history of SARS-CoV-2 infection nor history of SARS-CoV-2 vaccination). Immunogenicity Subset for Cohort B was a group of participants included in the study who had a negative anti-SARS-CoV-2 N-protein antibody test result at screening.

Cohort A and Cohort B could be started at the same time. Since S-268019-b was administered to the elderly participants for the first time, the administration of study intervention to the 11th and subsequent elderly participants were allowed when the first 10 elderly participants in Cohort A and Cohort B combined met both of the following criteria. If an event that met either of the following criteria occurred, the Data and Safety Monitoring Board was to confirm the safety results and then considered the acceptability of enrolling the 11th and subsequent participants.

- No serious treatment-related AEs (AEs considered “related” to the study intervention) occurred until 3 days after the first administration of study intervention (Day 4).
- Grade 3 or higher treatment-related AEs (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) occurred in more than 3 participants until 3 days after the first administration of study intervention (Day 4).

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If SARS-CoV-2 infection was suspected after the first administration of study intervention (if COVID-19 related symptoms listed in the table below [see Efficacy Assessment] were observed), COVID-19 Potential Illness Visit was to be made and, if the reverse transcription polymerase chain reaction (RT-PCR) test result was positive, COVID-19 Follow-up Visit was to be made on 28 days after COVID-19 Potential Illness Visit. COVID-19 Illness Visit was to be made by the participants who completed COVID-19 Potential Illness Visit if the investigator considered that additional testing was necessary (to be excluded the participants whose RT-PCR test result was negative at COVID-19 Potential Illness Visit).

Participants who wanted to have the third administration of study intervention could receive S-268019-b 10 μg on Day 211. However, the third administration of study intervention was prohibited in participants meeting any of the following criteria:

- The participant was found to be infected with SARS-CoV-2 by antigen test or RT-PCR test during the period from administration of study intervention on Day 29 to Day 211 pre-dose.
- The participant received any approved SARS-CoV-2 vaccine during the period from administration of study intervention on Day 29 to Day 211 pre-dose.
- The participant became pregnant during the period from administration of study intervention on Day 29 to Day 211 pre-dose and the pregnancy continued as of Day 211 pre-dose.
- A serious or intolerable AE occurred during the period from administration of study intervention on Day 29 to Day 211 pre-dose and the investigator or subinvestigator considered that the third administration of study intervention was not to be administered.
- Any of the following criteria was met during the period from administration of study intervention on Day 29 to Day 211 pre-dose and the investigator or subinvestigator considered that the third administration of study intervention was not to be administered:
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 5 × upper limit of normal (ULN)
  - ALT or AST ≥ 3 × ULN for ≥ 4 weeks
  - ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (direct bilirubin > 35%)
  - ALT or AST ≥ 3 × ULN and prothrombin time-international normalized ratio (PT-INR) > 1.5 if PT-INR was measured

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- ALT or AST ≥ 3 × ULN and at least weekly monitoring could not be performed for 4 weeks
- ALT or AST ≥ 3 × ULN, accompanied by the occurrence or worsening of symptoms believed to be related to liver disorder or hypersensitivity

In both Cohort A and Cohort B, the study was composed of the following 3 periods:

- Screening period (Day −28 to Day 1 pre-dose):

  Participants who had provided informed consent underwent screening investigations and examinations. Only those who were confirmed eligible for participation were enrolled.
- Evaluation period (Day 1 post-dose to Day 57 [28 ± 3 days after Visit 5]):

  Participants who were confirmed to be eligible to participate in the study on Day 1 pre-dose received 1 injection each of the study intervention as the primary vaccination via intramuscular injection at the study site on Day 1 and Day 29. The pre- and post-dose investigations/examinations were performed as scheduled. Scheduled investigations/examinations were also performed on Day 4 (only for the first 10 elderly participants), Day 8, Day 15 (only for participants whose cytokine-producing cell count was measured), Day 43, and Day 57.
- Follow-up period (Day 58 [the day after Visit 7] to Day 393 [364 ± 14 days after Visit 5]):

  Participants were to visit the study site on Days 97, 211, 225, 239, 302, and 393 (the visit on Day 225 was to be performed only for the participants receiving the third administration of study intervention who consented to the measurement of cytokine-producing cell count and T cell cytokine assay or who required the visit in the opinion of the investigator or subinvestigator; the visit on Day 239 was to be performed only for the participants who received the third administration of study intervention on Day 211) to undergo the scheduled investigations/examinations. Participants who wanted to have the third administration of study intervention as the booster vaccination received 1 injection of study intervention via intramuscular injection at the study site on Day 211.

Participants who received the third administration of study intervention on Day 211 entered Subpart for verification of noninferiority of immunogenicity after the booster

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vaccination compared to the primary vaccination with S-268019-b as well as for evaluation of the immunogenicity and safety and investigation of the clinical efficacy of the booster vaccination with S-268019-b.

Number of Participants (Planned and Analyzed):

Planned:

Cohort A: 3000 participants

Cohort B: 100 participants (only elderly participants with neither history of SARS-CoV-2 infection nor history of SARS-CoV-2 vaccination)

In Subpart, to verify the noninferiority of immunogenicity: ≥ 70 adult participants in Cohort A with neither history of SARS-CoV-2 infection nor history of SARS-CoV-2 vaccination and ≥ 70 participants in Cohort B.

Analyzed for immunogenicity:

- Immunogenicity Subset for Main Part: 563 participants (Naive: 304, Vaccination history: 76, Infection history: 68, Cohort B: 115).
- Immunogenicity Subset (Subpart): 389 participants (Naive: 207, Vaccination history: 54, Infection history: 50, Cohort B: 78).
- Immunogenicity Evaluable Subset (Subpart): 385 participants (Naive: 207, Vaccination history: 51, Infection history: 50, Cohort B: 77).

Analyzed for efficacy:

- Modified Intent to Treat (mITT) population: 3066 participants (Cohort A: 2951, Cohort B: 115).

Analyzed for safety:

- Safety Analysis population: 3278 participants (Naive: 2951, Vaccination history: 76, Infection history: 68, Cohort B: 118).

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).

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2. Exclusion criteria

- Tested positive for SARS-CoV-2 infection (as determined by SARS-CoV-2 antigen test) at screening.
- 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.
- Determined in the interview prior to the first administration of study intervention to have a history of SARS-CoV-2 infection (an exclusion criterion for Cohort B only).
- 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).
- Participant had a contraindication to intramuscular injections or blood draws.
- Previous SARS-CoV-2 vaccination with an investigational product.
- Received an approved SARS-CoV-2 vaccine less than 6 months ago (an exclusion criterion for Cohort A only).
- Previous SARS-CoV-2 vaccination with an approved product (an exclusion criterion for Cohort B only).
- Ineligible for participation in the study as considered by the investigator or subinvestigator.

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-910823 (antigen) is mixed with A-910823 (adjuvant, oil in water emulsion for injection) at a 1:1 ratio. A-910823 0.75 mL from the vial of 1 or 0.9 mL of A-910823 is taken, and then added to the vial filled with 0.75 mL of S-268019 for injection

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which contains S-910823 at 40 μg/mL. One injection (0.5 mL) was given in the upper arm intramuscularly at a 4-week interval for a total of 2 injections as the primary vaccination (Main Part). One injection (0.5 mL) was given in the upper arm intramuscularly as the booster vaccination (Subpart).

3. Packaging Lot Number

S-910823 (antigen): [redacted]

A-910823 (adjuvant): [redacted]

Duration of Treatment:

Maximum 3 days. Two days for the primary vaccination, where 1 injection each of S-268019-b was administered on Day 1 and Day 29, and 1 day for the booster vaccination, where 1 injection of the S-268019-b was administered on Day 211 only to willing participants.

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

Not applicable.

Criteria for Evaluation:

Immunogenicity and Other Immunological Indices Assessment:

There were no criteria set for immunogenicity or other immunological index evaluations. Measurements of SARS-CoV-2 neutralizing antibody titer and anti-spike protein IgG antibody titer, virology tests (SARS-CoV-2 antigen test, anti-SARS-CoV-2 N- and S-protein antibody tests, and genomic sequencing) were performed.

Efficacy Assessment:

Symptomatic COVID-19 was defined as a positive test result of RT-PCR and presence of at least 1 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
Not minimum duration	Fever (≥ 37.5°C), shortness of breath, difficulty breathing

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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

Severity of COVID-19

Severe COVID-19 is 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, percutaneous arterial oxygen saturation [SpO_2] ≤ 93% on room air at sea level, or arterial oxygen saturation [PaO_2]/fraction of inspiratory 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 COVID-19 onset who had tested positive for anti-SARS-CoV-2 N-protein antibody specified in schedule of activities (SoA) were treated as asymptomatic.

Safety Assessment:

A treatment-emergent adverse event (TEAE) was defined as an AE that occurred after the first administration of the study intervention. Treatment-related AEs were defined as AEs considered "related" to the study intervention.

Solicited AEs (solicited systemic AEs and solicited local AEs) were defined as any of the following AEs occurring within 7 days after each vaccination. Solicited systemic AEs, solicited local AEs, and unsolicited AEs (events other than solicited systemic AEs or solicited local AEs) considered "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:

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- Fever
- Nausea/vomiting
- Diarrhea
- Headache
- Fatigue
- Myalgia

- 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, home, etc.) because of the AE.

AESIs of S-268019-b were defined as potential immune-mediated diseases.

SAEs, MAAE, and AESI were collected from the date of signing the ICF until the end-of-study/early discontinuation examination, and other AEs were collected from the date of signing of the ICF until 28 days after the second administration of study intervention (Day 57)/early discontinuation examination and from after the third administration of study intervention (Day 211) until 28 days after the third administration (Day 239)/early discontinuation examination (only for the participants who received the third administration of study intervention). Physical examination, vital signs, 12-lead ECG, and laboratory tests 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 non-solicited AEs and SAEs was assessed and classified into 1 of the 5 categories.

Statistical Methods:

Immunogenicity Analyses:

The following immunogenicity analyses were performed for Immunogenicity Subset. In Subpart, analyses were performed for the Immunogenicity Subset (Subpart) and the supplementary analysis for the primary endpoint was performed for the Immunogenicity Evaluable Subset (Subpart).

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Primary Immunogenicity Endpoints for Subpart

The primary immunogenicity endpoints for Subpart were GMT and seroresponse rate of SARS-CoV-2 neutralizing antibody on Day 239 (28 days after the third administration). For participants receiving the third administration of study intervention included in the Immunogenicity Subset (Subpart), noninferiority testing was performed by comparing the log-transformed SARS-CoV-2 neutralizing antibody titer of Day 57 (28 days after the second administration) and Day 239 by paired t-test and estimating the ratio of GMT between these time points and its 95% confidence interval (CI). The test was performed separately for adult participants in Cohort A who had neither history of SARS-CoV-2 infection nor history of SARS-CoV-2 vaccination and for elderly participants in Cohort B. If the lower limit of the 95% CI exceeded 0.67, it was declared that the GMT 28 days after the third administration of study intervention was noninferior to that 28 days after the second administration of study intervention. Furthermore, noninferiority testing was performed by estimating the difference between the seroconversion rate for SARS-CoV-2 neutralizing antibody titer on Day 57 and the seroresponse rate for SARS-CoV-2 neutralizing antibody titer on Day 239 and its 95% CI by paired comparison test of proportions. The difference of the seroresponse rate after the third administration of study intervention from the seroconversion rate 28 days after the second administration of study intervention was tested with a noninferiority margin of −10%. Superiority of the GMT of SARS-CoV-2 neutralizing antibody on Day 239 to that on Day 57 was tested only if the noninferiority was confirmed for GMT and seroresponse rate. The superiority was to be declared if the lower limit of the 95% CI of the GMT ratio exceeds 1.0.

Secondary Immunogenicity Endpoints for Main Part and Subpart

The analysis methods for secondary immunogenicity endpoints were as follows:

- GMT of SARS-CoV-2 neutralizing antibody and 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.
- GMFR of SARS-CoV-2 neutralizing antibody titer and 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 participants who entered Subpart and received the third administration of study intervention, the pre-dose of the

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third administration was the baseline for evaluations after the third administration of study intervention.

- Seroconversion rate for SARS-CoV-2 neutralizing antibody titer and anti-spike protein IgG antibody titer at each time point

  The proportion of participants with a ≥ 4-fold rise from baseline in each antibody titer (seroconversion) and its 95% CI were calculated at each time point. The 95% CI for antibody titer seroconversion rate was calculated using the Clopper-Pearson method.
- Seroresponse rate for SARS-CoV-2 neutralizing antibody titer and anti-spike protein IgG antibody titer at each time point

  In participants who entered Subpart and received the third administration of study intervention, the proportion of participants with a ≥ 4-fold rise in each antibody titer from the value before the third administration (seroresponse rate) and its 95% CI were calculated at each time point. The 95% CI for seroresponse rate was calculated using the Clopper-Pearson method.

Efficacy Analyses:

The number of participants with symptomatic COVID-19 or asymptomatic COVID-19 14 days or later after the second administration of study intervention in mITT population were tabulated for each study intervention group. Number of participants with symptomatic COVID-19 or asymptomatic COVID-19 after the first administration of study intervention were also tabulated. Participants who entered Subpart and received the third administration of study intervention were censored at the time of the third administration of study intervention.

Furthermore, for participants in mITT population who entered Subpart and received the third administration of study intervention, the numbers of SARS-CoV-2-positive participants with COVID-19 onset and asymptomatic SARS-CoV-2-positive participants who were first confirmed at or after 14 days after the third administration of study intervention were tabulated. Similarly, the numbers of SARS-CoV-2-positive participants with COVID-19 onset and asymptomatic SARS-CoV-2-positive participants who were first confirmed at or after the third administration of study intervention were tabulated. In addition, the genome sequences of SARS-CoV-2 variants were listed for participants who had a symptomatic COVID-19.

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Safety Analyses:

The following safety analyses were performed for the Safety Analysis population. Furthermore, safety analysis was performed on the participants in Safety Analysis population who entered Subpart and received the third administration of study intervention, using the pre-dose data of the third administration as baseline.

For safety analyses as Main Part, the data collected from participants who did not receive the third administration, or until the third administration were used (these participants were defined as the Safety Analysis population for Main Part). For safety analyses as Subpart, the data collected after the third administration were used (these participants were defined as the Safety Analysis population for Subpart).

AEs were coded and classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0. The number and percentage of participants with TEAEs, TEAE leading to death, other serious TEAEs, MAAEs, AESIs, TEAE leading to discontinuation, solicited systemic AEs, solicited local AEs, and unsolicited AEs were summarized by cohort and subgroup. The incidences and their 95% CIs were calculated by using the Clopper-Pearson method. Treatment-related AEs were summarized in the same manner as TEAEs.

Summary statistics for laboratory test results, vital signs, 12-lead ECG measurements, and the change from baseline at each scheduled time point were presented by cohort and subgroup.

Summary of Results:

Immunogenicity:

Primary Vaccination (Main Part)

In the Immunogenicity Subset for Main Part, the proportions of the male participants were 42.8% in Naive, 47.4% in Vaccination History, 67.6% in Infection History, and 60.9% in Elderly Naive (Cohort B) (hereinafter the same order). The median ages (min-max) of the participants were 47.0 (20-63) years, 42.5 (24-62) years, 39.0 (21-64) years, and 69.0 (65-82) years. The mean body mass indices (BMIs) (standard deviation [SD]) were 23.32 (3.95), 23.50 (3.88), 24.03 (4.44), and 23.52 (3.82).

1. Secondary Immunogenicity Endpoints

- GMT of SARS-CoV-2 neutralizing antibody at each time point

  The GMTs (95% CI) of SARS-CoV-2 neutralizing antibody in Naive, Vaccination History, Infection History, and Elderly Naive (Cohort B) (hereinafter the same order) were 2.52 (2.50 to 2.54), 5.33 (4.51 to 6.30), 6.01

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(4.72 to 7.64), and 2.53 (2.47 to 2.59) at baseline, respectively; 46.14 (41.91 to 50.80), 106.54 (89.70 to 126.55), 125.67 (105.70 to 149.40), and 26.56 (21.72 to 32.47) on Day 43, respectively; 30.72 (27.97 to 33.73), 108.09 (92.10 to 126.87), 117.99 (98.84 to 140.86), and 20.38 (16.89 to 24.60) on Day 57, respectively; 3.97 (2.92 to 5.40), 16.25 (11.62 to 22.70), 36.23 (16.63 to 78.94), and 3.30 (2.49 to 4.38) on Day 393, respectively.

In Naive and Elderly Naive (Cohort B), the GMTs of SARS-CoV-2 neutralizing antibody peaked on Day 43 (14 days after the second administration) and then decreased gradually. In Vaccination History and Infection History, the GMTs of SARS-CoV-2 neutralizing antibody increased to a higher level than that of Naive, and the subsequent decrease was more gradual.

- GMFR of SARS-CoV-2 neutralizing antibody titer at each time point

  The GMFRs (95% CI) of SARS-CoV-2 neutralizing antibody titer in Naive, Vaccination History, Infection History, and Elderly Naive (Cohort B) (hereinafter the same order) were 18.33 (16.67 to 20.15), 19.97 (16.30 to 24.48), 20.37 (15.17 to 27.36), and 10.49 (8.59 to 12.81) on Day 43, respectively; 12.20 (11.13 to 13.38), 20.28 (16.81 to 24.46), 19.13 (14.18 to 25.80), and 8.05 (6.67 to 9.72) on Day 57, respectively; 1.59 (1.17 to 2.16), 3.03 (2.14 to 4.29), 9.75 (4.78 to 19.90), and 1.32 (0.99 to 1.75) on Day 393, respectively.
- Seroconversion rate for SARS-CoV-2 neutralizing antibody titer at each time point

  The seroconversion rates (95% CI) for SARS-CoV-2 neutralizing antibody titer in Naive, Vaccination History, Infection History, and Elderly Naive (Cohort B) (hereinafter the same order) were 96.6% (93.9% to 98.4%), 98.7% (92.8% to 100.0%), 95.5% (87.3% to 99.1%), and 85.5% (77.5% to 91.5%) on Day 43, respectively; 95.9% (93.0% to 97.9%), 100.0% (95.3% to 100.0%), 97.0% (89.5% to 99.6%), and 85.5% (77.5% to 91.5%) on Day 57, respectively; 12.5% (2.7% to 32.4%), 70.0% (34.8% to 93.3%), 85.7% (42.1% to 99.6%), and 13.3% (1.7% to 40.5%) on Day 393, respectively.
- GMT of anti-spike protein IgG antibody at each time point

  The GMTs (95% CI) of anti-spike protein IgG antibody in Naive, Vaccination History, Infection History, and Elderly Naive (Cohort B) (hereinafter the same order) were 61.7 (57.9 to 65.7), 2028.2 (1681.4 to 2446.4), 1616.4 (1154.9 to 2262.3), and 53.1 (48.7 to 58.0) at baseline, respectively; 32430.7 (29448.8 to

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35714.5), 26564.1 (21649.2 to 32594.8), 30284.3 (24834.3 to 36930.2), and 12880.9 (10083.1 to 16455.1) on Day 43, respectively; 29213.2 (26314.9 to 32430.7), 44653.6 (38151.3 to 52264.0), 65877.2 (54707.7 to 79327.2), and 27093.8 (22548.2 to 32555.7) on Day 57, respectively; 1037.5 (623.5 to 1726.4), 5571.5 (3768.0 to 8238.3), 7801.7 (2790.9 to 21808.8), and 552.8 (260.6 to 1172.6) on Day 393, respectively.

In Naive and Elderly Naive (Cohort B), the GMTs of anti-spike protein IgG antibody peaked on Day 43 to 57 (14 to 28 days after the second administration) and then decreased gradually. In Vaccination History and Infection History, the GMTs of anti-spike protein IgG antibody increased to a higher level than that of Naive, and the subsequent decrease was more gradual.

- GMFR of anti-spike protein IgG antibody titer at each time point

  The GMFRs (95% CI) of anti-spike protein IgG antibody titer in Naive, Vaccination History, Infection History, and Elderly Naive (Cohort B) (hereinafter the same order) were 529.06 (473.70 to 590.90), 13.06 (10.21 to 16.69), 18.34 (13.14 to 25.59), and 241.89 (186.01 to 314.54) on Day 43, respectively; 475.91 (423.52 to 534.79), 22.02 (18.07 to 26.83), 39.90 (27.83 to 57.19), and 508.78 (415.76 to 622.62) on Day 57, respectively; 19.58 (11.98 to 32.03), 3.03 (1.78 to 5.17), 6.56 (2.35 to 18.35), and 11.06 (5.21 to 23.45) on Day 393, respectively.
- Seroconversion rate for anti-spike protein IgG antibody titer at each time point

  The seroconversion rates (95% CI) for anti-spike protein IgG antibody titer in Naive, Vaccination History, Infection History, and Elderly Naive (Cohort B) (hereinafter the same order) were 99.7% (98.1% to 100.0%), 92.0% (83.4% to 97.0%), 93.9% (85.2% to 98.3%), and 99.1% (95.0% to 100.0%) on Day 43, respectively; 100.0% (98.8% to 100.0%), 100.0% (95.3% to 100.0%), 95.5% (87.3% to 99.1%), and 100.0% (96.7% to 100.0%) on Day 57, respectively; 95.8% (78.9% to 99.9%), 40.0% (12.2% to 73.8%), 85.7% (42.1% to 99.6%), and 80.0% (51.9% to 95.7%) on Day 393, respectively.

2. Exploratory Immunogenicity Endpoints

- The interferon-gamma (IFN-γ)-producing cells increased after the second injection with S-268019-b in all cohorts (Vaccination History, Infection History, and Elderly Naive [Cohort B]).
- The second 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

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produce IL-4 or IL-5) in all cohorts (Vaccination History, Infection History, and Elderly Naive [Cohort B]).

Booster Vaccination (Subpart)

In the Immunogenicity Subset (Subpart), the proportions of the male participants were 47.3% in Naive, 48.1% in Vaccination History, 68.0% in Infection History, and 60.3% in Elderly Naive (Cohort B) (hereinafter the same order). The median ages (min-max) of the participants were 48.0 (20-63) years, 43.5 (25-62) years, 42.5 (21-64) years, and 69.0 (65-82) years, respectively. The mean BMIs (SD) were 23.13 (3.96), 23.83 (4.04), 24.55 (4.32), and 23.63 (4.05), respectively.

1. Primary Immunogenicity Endpoints

Both the GMTs of the SARS-CoV-2 neutralizing antibody and the seroresponse rates of 28 days after the third administration, which were the primary immunogenicity endpoints, were confirmed to be noninferior to those of 28 days after the second administration both in Naive and Elderly Naive (Cohort B). Since noninferiority for both the GMT and the seroresponse rate of the SARS-CoV-2 neutralizing antibody was confirmed, the superiority test for the GMT of the SARS-CoV-2 neutralizing antibody was then performed, and superiority for the GMT of 28 days after the third administration of study intervention to that of 28 days after the second administration of study intervention was also shown both in Naive and Elderly Naive (Cohort B) ($p < 0.0001$). The GMTs of SARS-CoV-2 neutralizing antibody in Naive and Elderly Naive (Cohort B) increased approximately 5-fold 28 days after the third administration of study intervention (Day 239) compared to those of 28 days after the second administration (Day 57).

2. Secondary Immunogenicity Endpoints

- GMT of SARS-CoV-2 neutralizing antibody at each time point

  The GMTs (95% CI) of SARS-CoV-2 neutralizing antibody in Naive, Vaccination History, Infection History, and Elderly Naive (Cohort B) (hereinafter the same order) were 4.97 (4.45 to 5.54), 43.62 (34.67 to 54.89), 50.63 (38.70 to 66.24), and 3.55 (3.06 to 4.13) on Day 211 (baseline), respectively; 154.16 (138.40 to 171.71), 107.67 (85.25 to 135.99), 173.88 (138.04 to 219.02), and 113.14 (95.24 to 134.40) on Day 239, respectively; 49.31 (42.59 to 57.09), 29.09 (22.33 to 37.90), 71.99 (57.96 to 89.42), and 26.84 (20.86 to 34.53) on Day 393, respectively.

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The GMTs of SARS-CoV-2 neutralizing antibody peaked on Day 239 (28 days after the third administration) and then decreased gradually in all cohorts and subgroups.

- GMFR of SARS-CoV-2 neutralizing antibody titer at each time point

  The GMFRs (95% CI) of SARS-CoV-2 neutralizing antibody titer in Naive, Vaccination History, Infection History, and Elderly Naive (Cohort B) (hereinafter the same order) were 30.92 (26.90 to 35.54), 2.41 (1.97 to 2.95), 3.43 (2.65 to 4.45), and 32.00 (25.93 to 39.50) on Day 239, respectively; 19.17 (16.45 to 22.34), 1.26 (1.05 to 1.51), 2.00 (1.50 to 2.66), and 14.37 (11.24 to 18.38) on Day 302, respectively; 10.28 (8.82 to 11.98), 0.69 (0.55 to 0.88), 1.33 (1.04 to 1.71), and 7.58 (5.90 to 9.75) on Day 393, respectively.
- Seroresponse rate for SARS-CoV-2 neutralizing antibody titer at each time point

  The seroresponse rates (95% CI) for SARS-CoV-2 neutralizing antibody titer in Naive, Vaccination History, Infection History, and Elderly Naive (Cohort B) (hereinafter the same order) were 96.5% (93.0% to 98.6%), 37.5% (24.0% to 52.6%), 58.0% (43.2% to 71.8%), and 97.4% (90.9% to 99.7%) on Day 239, respectively; 95.7% (91.6% to 98.1%), 7.7% (1.6% to 20.9%), 34.8% (21.4% to 50.2%), 94.4% (86.2% to 98.4%) on Day 302, respectively; 91.6% (86.3% to 95.3%), 2.8% (0.1% to 14.5%), 19.6% (9.4% to 33.9%), and 86.2% (75.3% to 93.5%) on Day 393, respectively.
- GMT of anti-spike protein IgG antibody at each time point

  The GMTs (95% CI) of anti-spike protein IgG antibody in Naive, Vaccination History, Infection History, and Elderly Naive (Cohort B) (hereinafter the same order) were 2885.5 (2528.4 to 3293.0), 17586.6 (13571.8 to 22789.1), 18101.9 (13769.5 to 23797.6), and 1985.9 (1556.2 to 2534.1) on Day 211 (baseline), respectively; 95704.2 (85341.9 to 107324.8), 40256.0 (31925.1 to 50760.9), 48438.2 (39413.4 to 59529.4), and 59022.8 (48074.3 to 72464.6) on Day 239, respectively; 18064.8 (15199.5 to 21470.3), 9484.9 (6793.4 to 13242.9), 16537.1 (13072.1 to 20920.7), and 10934.4 (8276.7 to 14445.4) on Day 393, respectively.

  In all cohorts and subgroups, the GMTs of anti-spike protein IgG antibody peaked on Day 239 (28 days after the third administration) and then decreased gradually.

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- GMFR of anti-spike protein IgG antibody titer at each time point

  The GMFRs (95% CI) of anti-spike protein IgG antibody titer in Naive, Vaccination History, Infection History, and Elderly Naive (Cohort B) (hereinafter the same order) were 32.90 (28.25 to 38.30), 2.28 (1.94 to 2.67), 2.68 (2.12 to 3.38), and 30.05 (23.87 to 37.81) on Day 239, respectively; 13.66 (11.60 to 16.08), 0.97 (0.76 to 1.23), 1.41 (1.02 to 1.96), and 12.78 (9.83 to 16.62) on Day 302, respectively; 6.10 (5.10 to 7.29), 0.54 (0.44 to 0.67), 0.85 (0.66 to 1.08), and 5.51 (4.18 to 7.26) on Day 393, respectively.
- Seroresponse rate for anti-spike protein IgG antibody titer at each time point

  The seroresponse rates (95% CI) for anti-spike protein IgG antibody titer in Naive, Vaccination History, Infection History, and Elderly Naive (Cohort B) (hereinafter the same order) were 98.0% (95.0% to 99.5%), 27.1% (15.3% to 41.8%), 38.0% (24.7% to 52.8%), and 97.4% (90.9% to 99.7%) on Day 239, respectively; 92.4% (87.6% to 95.8%), 2.6% (0.1% to 13.5%), 17.4% (7.8% to 31.4%), and 95.8% (88.1% to 99.1%) on Day 302, respectively; 75.9% (68.7% to 82.2%), 0.0% (0.0% to 9.7%), 6.5% (1.4% to 17.9%), and 72.3% (59.8% to 82.7%) on Day 393, respectively.

3. Exploratory Immunogenicity Endpoints

- The IFN-γ-producing cells increased after the booster injection with S-268019-b in both cohorts (Infection History and Elderly Naive [Cohort B]).
- The 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) in both cohorts (Infection History and Elderly Naive [Cohort B]).

Efficacy:

In the mITT population for Main Part, the proportions of the male participants were 53.2% in Adult Naive (Cohort A) and 60.9% in Elderly Naive (Cohort B) (hereinafter the same order). The median ages (min-max) of the participants were 46.0 (20-64) years and 69.0 (65-82) years. The mean BMIs (SD) were 23.33 (3.97) and 23.52 (3.82).

The number of symptomatic participants with SARS-CoV-2 infection contracted for the first time from 14 days after the second administration of study intervention was 209 of 3066 (204 of 2951 in Adult Naive [Cohort A] and 5 of 115 in Elderly Naive [Cohort B]). The number of asymptomatic participants with SARS-CoV-2 infection contracted for the first time from 14 days after the second administration of study

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intervention was 215 of 3066 (210 of 2951 in Adult Naive [Cohort A] and 5 of 115 in Elderly Naive [Cohort B]).

The number of symptomatic participants with SARS-CoV-2 infection contracted for the first time after the first administration of study intervention was 209 of 3066 (204 of 2951 in Adult Naive [Cohort A] and 5 of 115 in Elderly Naive [Cohort B]). The number of asymptomatic participants with SARS-CoV-2 infection contracted for the first time after the first administration of study intervention was 216 of 3066 (211 of 2951 in Adult Naive [Cohort A] and 5 of 115 in Elderly Naive [Cohort B]).

In the mITT population for Subpart, the proportions of the male participants were 55.8% in Adult Naive (Cohort A) and 62.8% in Elderly Naive (Cohort B) (hereinafter the same order). The median ages (min-max) of the participants were 47.0 (20-64) years and 68.5 (65-82) years. The mean BMIs (SD) were 23.45 (3.99) and 23.71 (4.10).

The number of symptomatic participants with SARS-CoV-2 infection contracted for the first time from 14 days after the third administration of study intervention was 135 of 2223 (131 of 2137 in Adult Naive [Cohort A] and 4 of 86 in Elderly Naive [Cohort B]). The number of asymptomatic participants with SARS-CoV-2 infection contracted for the first time from 14 days after the third administration of study intervention was 250 of 2223 (243 of 2137 in Adult Naive [Cohort A] and 7 of 86 in Elderly Naive [Cohort B]).

The number of symptomatic participants with SARS-CoV-2 infection contracted for the first time after the third administration of study intervention was 136 of 2223 (132 of 2137 in Adult Naive [Cohort A] and 4 of 86 in Elderly Naive [Cohort B]). The number of asymptomatic participants with SARS-CoV-2 infection contracted for the first time after the third administration of study intervention was 250 of 2223 (243 of 2137 in Adult Naive [Cohort A] and 7 of 86 in Elderly Naive [Cohort B]).

A total of 78 genome data of SARS-CoV-2, including 9 for “Unable to be analyzed,” were obtained in this study. The most common genome types of SARS-CoV-2 were BA.1.1.2 and BA.5.2 (14.1%, 11 of 78, each), followed by BF.5 (11.5%, 9 of 78) and BA.5.2.1 (10.3%, 8 of 78).

The analysis by date showed that, before 20 May 2022, BA.1 lineage accounted for 48.0% (12 of 25) of the total. After 21 May 2022, BA.5 and BF.5 lineage accounted for 58.5% (31 of 53) and 17.0% (9 of 53) of the total, respectively.

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Safety:

Primary Vaccination (Main Part)

In the Safety Analysis population for Main Part, the proportions of the male participants were 53.5% in Cohort A (53.2% in Naive, 47.4% in Vaccination History, and 67.6% in Infection History) and 60.2% in Cohort B. The median ages (min-max) of the participants were 46.0 (20-80) in Cohort A (46.0 [20-64] years in Naive, 42.5 [24-62] years in Vaccination History, and 39.0 [21-64] years in Infection History) and 69.0 (65-82) years in Cohort B. The mean BMIs (SD) were 23.34 (3.98) in Cohort A (23.33 [3.97] in Naive, 23.50 [3.88] in Vaccination History, and 24.03 [4.44] in Infection History) and 23.50 (3.83) in Cohort B.

There were no significant findings of safety concern for Main Part.

In the Safety Analysis population for Main Part, a total of 21,230 AEs were reported in 3084 of 3160 participants (97.6%) in Cohort A (19,724 events were reported in 2879 of 2951 participants [97.6%] in Naive, 524 events were reported in 75 of 76 participants [98.7%] in Vaccination History, and 507 events were reported in 67 of 68 participants [98.5%] in Infection History) and 605 events were reported in 109 of 118 participants (92.4%) in Cohort B. Most of the AEs in each cohort or subgroup were solicited AEs and considered related to the study intervention.

In the Safety Analysis population for Main Part, a total of 9712 solicited systemic AEs were reported in 2567 of 3160 participants (81.2%) in Cohort A (9012 events were reported in 2389 of 2951 participants [81.0%] in Naive, 235 events were reported in 61 of 76 participants [80.3%] in Vaccination History, and 251 events were reported in 61 of 68 participants [89.7%] in Infection History) and 170 events were reported in 64 of 118 participants (54.2%) in Cohort B. Of these, most of events were considered related to the study intervention. In 3 subgroups of Cohort A and in Cohort B, the most common solicited systemic AE was fatigue. None of the participants reported Grade 5 solicited systemic AEs and most of the reported solicited systemic AEs were Grade 1 or Grade 2 in severity. A Grade 4 solicited systemic AE was fever (> 40°C) reported in Naive after the second administration of study intervention. Most of the solicited systemic AEs occurred within 4 days after the first administration of study intervention and resolved within 6 days.

In the Safety Analysis population for Main Part, a total of 10,029 solicited local AEs were reported in 3021 of 3160 participants (95.6%) in Cohort A (9358 events were reported in 2817 of 2951 participants [95.5%] in Naive, 234 events were reported in 75 of 76 participants [98.7%] in Vaccination History, and 209 events were reported in

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66 of 68 participants [97.1%] in Infection History) and 351 events were reported in 98 of 118 participants (83.1%) in Cohort B. Of these, most of events were considered related to the study intervention. In 3 subgroups of Cohort A and in Cohort B, the most common solicited local AE was pain. None of the participants reported Grade 5 or Grade 4 solicited local AEs. Most of the reported solicited local AEs were Grade 1 or Grade 2 in severity. Most of the solicited local AEs occurred within 3 days after the first administration of study intervention and resolved within 7 days.

In the Safety Analysis population for Main Part, a total of 1489 unsolicited AEs were reported in 943 of 3160 participants (29.8%) in Cohort A (1354 events were reported in 868 of 2951 participants [29.4%] in Naive, 55 events were reported in 34 of 76 participants [44.7%] in Vaccination History, and 47 events were reported in 27 of 68 participants [39.7%] in Infection History) and 84 events were reported in 54 of 118 participants (45.8%) in Cohort B. Of these, 328 events reported in 250 of 3160 participants (7.9%) in Cohort A (303 events reported in 234 of 2951 participants [7.9%] in Naive, 3 events reported in 3 of 76 participants [3.9%] in Vaccination History, and 18 events reported in 10 of 68 participants [14.7%] in Infection History) and 21 events reported in 18 of 118 participants (15.3%) in Cohort B were considered related to the study intervention.

In the Safety Analysis population for Main Part, 1 participant in Cohort B died from cardiac failure acute. The cardiac failure acute was considered unrelated to the study intervention by the investigator.

In the Safety Analysis population for Main Part, a total of 41 nonfatal SAEs were reported: 34 nonfatal SAEs in 32 participants in Naive, 2 nonfatal SAEs in 2 participants in Infection History, 1 nonfatal SAE in 1 participant in Elderly Other and 4 nonfatal SAEs in 4 participants in Cohort B. All nonfatal SAEs were considered unrelated to the study intervention by the investigators.

In the Safety Analysis population for Main Part, a total of 17 AEs leading to discontinuation of study intervention were reported in 12 of 3160 participants (0.4%) in Cohort A (10 events were reported in 10 of 2951 participants [0.3%] in Naive, no events were reported in Vaccination History, and 7 events were reported in 2 of 68 participants [2.9%] in Infection History) and 7 events were reported in 1 of 118 participants (0.8%) in Cohort B. Except for 4 events reported in Naive, all events were considered related to the study intervention. AEs leading to discontinuation of study intervention that occurred after the first and the second administration of study intervention were as follows: a total of 23 events leading to discontinuation of study intervention that occurred after the first administration were reported in

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12 participants, and 1 event leading to discontinuation of study intervention that occurred after the second administration was reported in 1 participant.

In the Safety Analysis population for Main Part, 6 AESIs were reported: 5 AESIs in 5 participants in Naive and 1 AESI in 1 participant in Cohort B were reported. None of the AESIs were serious. Except 1 Grade 1 treatment-related AESI, all other AESIs were considered unrelated to the study intervention.

In the Safety Analysis population for Main Part, the incidences of MAAEs were 20.0% (632 of 3160 participants) in Cohort A (19.4% [572 of 2951 participants] in Naive, 36.8% [28 of 76 participants] in Vaccination History, and 32.4% [22 of 68 participants] in Infection History) and 27.1% (32of 118 participants) in Cohort B. The incidences of treatment-related MAAEs were 2.4% (77 of 3160 participants) in Cohort A (2.3% [69 of 2951 participants] in Naive, 1.3% [1 of 76 participants] in Vaccination History, and 8.8% [6 of 68 participants] in Infection History), and 4.2% (5 of 118 participants) in Cohort B.

No apparent trends related to the S-268019-b administration were found in clinical laboratory tests, vital signs, or ECG parameters for both Main Part and Subpart.

Thus, no serious or significant findings clearly related to S-268019-b were found during the follow-up until 1 year after the second administration. The safety of S-268019-b for Main Part was considered generally acceptable.

Booster Vaccination (Subpart)

In the Safety Analysis population for Subpart, the proportions of the male participants were 56.1% in Cohort A (55.8% in Naive, 49.1% in Vaccination History, and 68.6% in Infection History) and 62.5% in Cohort B. The median ages (min-max) of the participants were 47.0 (20-80) years in Cohort A (47.0 [20-64] years in Naive, 44.0 [25-62] years in Vaccination History, and 42.0 [21-64] years in Infection History) and 68.5 (65-82) years in Cohort B. The mean BMIs (SD) were 23.47 (3.99) in Cohort A (23.45 [3.99] in Naive, 23.86 [4.01] in Vaccination History, and 24.58 [4.29] in Infection History) and 23.70 (4.11) in Cohort B.

There were no significant findings of safety concern for Subpart. The safety of the third administration of study intervention was consistent with that of the second administration.

In the Safety Analysis population for Subpart, a total of 11,100 AEs were reported in 2183 of 2291 participants (95.3%) in Cohort A (10,500 events were reported in 2034 of 2137 participants [95.2%] in Naive, 170 events were reported in 52 of 55 participants [94.5%] in Vaccination History, and 238 events were reported in 50 of

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51 participants [98.0%] in Infection History) and 333 events were reported in 78 of 88 participants (88.6%) in Cohort B. The incidence of AEs in Cohort B was lower than that in Naive. All of solicited AEs were considered related to the study intervention.

In the Safety Analysis population for Subpart, a total of 6024 solicited systemic AEs were reported in 1917 of 2291 participants (83.7%) in Cohort A (5707 events were reported in 1804 of 2137 participants [84.4%] in Naive, 91 events were reported in 39 of 55 participants [70.9%] in Vaccination History, and 129 events were reported in 40 of 51 participants [78.4%] in Infection History) and 119 events were reported in 49 of 88 participants (55.7%) in Cohort B. All of solicited local AEs were considered related to the study intervention. In 3 subgroups of Cohort A and in Cohort B, the most common solicited systemic AE was fatigue. None of the participants reported Grade 5 solicited systemic AEs and most of the reported solicited systemic AEs were Grade 1 or Grade 2 in severity. In Naive, 3 participants reported Grade 4 fever (> 40°C) after the third administration of study intervention. Most of the solicited systemic AEs occurred within 3 days after the third administration of study intervention and resolved within 7 days.

In the Safety Analysis population for Subpart, a total of 4629 solicited local AEs were reported in 2084 of 2291 participants (91.0%) in Cohort A (4372 events were reported in 1940 of 2137 participants [90.8%] in Naive, 72 events were reported in 51 of 55 participants [92.7%] in Vaccination History, and 96 events were reported in 48 of 51 participants [94.1%] in Infection History) and 185 events were reported in 73 of 88 participants (83.0%) in Cohort B. All of solicited local AEs were considered related to the study intervention. In 3 subgroups of Cohort A and in Cohort B, the most common solicited local AE was pain. None of the participants reported Grade 5 or Grade 4 solicited local AEs. Most of the reported solicited local AEs were Grade 1 or Grade 2 in severity. Most of the solicited local AEs occurred within 3 days after the first administration of study intervention and resolved within 7 days.

In the Safety Analysis population for Subpart, a total of 447 unsolicited AEs were reported in 350 of 2291 participants (15.3%) in Cohort A (421 events were reported in 328 of 2137 participants [15.3%] in Naive, 7 events were reported in 6 of 55 participants [10.9%] in Vaccination History, and 13 events were reported in 10 of 51 participants [19.6%] in Infection History) and 29 events were reported in 21 of 88 participants (23.9%) in Cohort B. Of these, 100 events reported in 91 of 2291 participants (4.0%) in Cohort A (98 events reported in 89 of 2137 participants [4.2%] in Naive, no events reported in Vaccination History, and 2 events reported in 2

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of 51 participants [3.9%] in Infection History) and 5 events reported in 5 of 88 participants (5.7%) in Cohort B were considered related to the study intervention.

In the Safety Analysis population for Subpart, no deaths were reported.

In the Safety Analysis population for Subpart, a total of 17 nonfatal SAEs were reported after the third administration of study intervention: 11 nonfatal SAEs in 11 participants in Naive, 1 nonfatal SAE in 1 participant in Elderly Other, and 5 nonfatal SAEs in 4 participants in Cohort B. All nonfatal SAEs were considered unrelated to the study intervention by the investigators.

In the Safety Analysis population for Subpart, 1 AESI of gout in 1 participant in Naive was reported. The AE was not serious and considered unrelated to the study intervention.

In the Safety Analysis population for Subpart, the incidences of MAAEs were 11.2% (256 of 2291 participants) in Cohort A (11.0% [236 of 2137 participants] in Naive, 10.9% [6 of 55 participants] in Vaccination History, and 15.7% [8 of 51 participants] in Infection History) and 20.5% (18 of 88 participants) in Cohort B. The incidences of treatment-related MAAEs were 1.0% (23 of 2291 participants) in Cohort A (1.0% [22 of 2137 participants] in Naive, 0% in Vaccination History, and 2.0% [1 of 51 participants] in Infection History) and 2.3% (2 of 88 participants) in Cohort B.

No apparent trends related to the S-268019-b administration were found in clinical laboratory tests, vital signs, or ECG parameters for both Main Part and Subpart.

Thus, no serious or significant findings clearly related to S-268019-b were found during the follow-up until 6 months after the third administration. The safety of S-268019-b for Subpart was considered generally acceptable.

Conclusions:

This Phase 2/3 clinical study (Study 2114U0222) was multicenter, uncontrolled, open-label study in adult (20 to 64 years) and elderly (65 years or older) participants, consisting of 2 cohorts (A and B); Cohort B were enrolled by only elderly participants.

Primary Vaccination (Main Part)

1. Immunogenicity

The GMTs, GMFRs, and seroconversion rates of SARS-CoV-2 neutralizing antibody and anti-spike protein IgG antibody increased from Baseline to Day 43 (14 days after the second administration of study intervention) and Day 57 (28 days after the second administration of study intervention) in all cohorts and subgroups.

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From the immunogenicity assessments, we concluded that the SARS-CoV-2 neutralizing antibody titer and anti-spike protein IgG antibody titer increased in all cohorts and subgroups up to Day 57 (28 days after the second administration of study intervention).

2. Clinical Efficacy

The number of symptomatic participants with SARS-CoV-2 infection contracted for the first time from 14 days after the second administration of study intervention was 209 of 3066 (204 of 2951 in Adult Naive [Cohort A] and 5 of 115 in Elderly Naive [Cohort B]). The number of asymptomatic participants with SARS-CoV-2 infection contracted for the first time from 14 days after the second administration of study intervention was 215 of 3066 (210 of 2951 in Adult Naive [Cohort A] and 5 of 115 in Elderly Naive [Cohort B]).

The numbers of symptomatic and asymptomatic participants with SARS-CoV-2 infection contracted for the first time after the first administration of study intervention were the same as those after 14 days or later of the second administration of study intervention, except there was 1 additional asymptomatic participant reported after the first administration in Adult Naive [Cohort A].

3. Safety

From the safety assessments, we conclude that AEs occurred in most of the participants who received S-268019-b at least once. However, AEs reported after vaccination of S-268019-b and the incidence were almost the same as those of other approved SARS-CoV-2 vaccines. Thus, no significant safety concerns were identified and the safety of S-268019-b was considered generally acceptable in any of subgroups or cohort.

Booster Vaccination (Subpart)

1. Immunogenicity

Both the GMTs of the SARS-CoV-2 neutralizing antibody and the seroresponse rates of 28 days after the third administration, which were the primary immunogenicity endpoints, were confirmed to be noninferior to those of 28 days after the second administration both in Naive and Elderly Naive (Cohort B). Since noninferiority for both the GMT and the seroresponse rate of the SARS-CoV-2 neutralizing antibody was confirmed, the superiority test for the GMT of the SARS-CoV-2 neutralizing antibody was then performed, and superiority for the GMT of 28 days after the third administration of study intervention to that of 28 days after the second administration of study intervention was also shown both in Naive and Elderly Naive (Cohort B)

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($p < 0.0001$). The GMTs of SARS-CoV-2 neutralizing antibody in Naive and Elderly Naive (Cohort B) increased approximately 5-fold 28 days after the third administration of study intervention (Day 239) compared to those of 28 days after the second administration (Day 57). The GMTs of anti-spike protein IgG antibody increased similarly to the SARS-CoV-2 neutralizing antibody titer after the third administration of study intervention.

From the immunogenicity assessments, we concluded that the SARS-CoV-2 neutralizing antibody titer and anti-spike protein IgG antibody titer increased in all cohorts and subgroups after the third administration of study intervention.

2. Clinical Efficacy

The number of symptomatic participants with SARS-CoV-2 infection contracted for the first time from 14 days after the third administration of study intervention was 135 of 2223 (131 of 2137 in Adult Naive [Cohort A] and 4 of 86 in Elderly Naive [Cohort B]). The number of asymptomatic participants with SARS-CoV-2 infection contracted for the first time from 14 days after the third administration of study intervention was 250 of 2223 (243 of 2137 in Adult Naive [Cohort A] and 7 of 86 in Elderly Naive [Cohort B]).

The numbers of symptomatic and asymptomatic participants with SARS-CoV-2 infection contracted for the first time after the third administration of study intervention were the same as those after 14 days or later of the third administration of study intervention, except there was 1 additional symptomatic participant reported after the third administration in Adult Naive [Cohort A].

3. Safety

No significant safety concerns were identified specific to the third administration and the safety of S-268019-b was considered generally acceptable in any of subgroups or cohort.

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