Statistical Analysis Plan

Study Title:	A Phase 3, Randomized, Observer-Blind, Placebo-Controlled Cross-over Study to Evaluate the Efficacy, Safety, and Immunogenicity of S-268019 for the Prevention of COVID-19
Study Number:	2126U0232
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SIGNATURE PAGE

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RECORDS ON REVISIONS

Document History

Version	Date	Author	Memo
1.0	2022/03/07	[redacted]	Originally prepared
2.0	2022/07/20	[redacted]	Deletion of description about interim analysis Review of analysis items and categories Improvement of description More detailed analysis methods
3.0	2022/12/13	[redacted]	The last date of efficacy evaluation in the Initial Vaccination Period was specified as censoring reason for symptomatic and asymptomatic COVID-19 in 9.1 and 9.2. Description about analyses prior to study completion was added as Section 13. Description adjustment
4.0	2023/9/25	[redacted]	In 6.5.2 Baseline, remove the definition of crossover vaccination period baseline. Add to section 7.2 that the safety analysis population table should also be prepared for subjects who received the investigational drug during the crossover vaccination period. Add to Table 4 that the tabulation for the crossover vaccination period outputs the results of anti-SARS-CoV-2 N-protein antibody test immediately before the crossover vaccination. Add to section 10 the details of endpoints and analysis method. Listing of genome sequences was added to Section 10.2. In Prior and Concomitant Drugs and Therapies, Immunogenicity Endpoint, and Vital Signs, remove analysis by intervention period Description adjustment

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body mass index
CI	Confidence interval
CRF	Case report form
DSMB	Data safety monitoring board
ECG	Electrocardiogram
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMT	Geometric mean titer
GMFR	Geometric mean fold rise
IgG	Immunoglobulin G
IWRS	Interactive Web Response System
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
TFL	Table, figure, and listing
ULN	Upper limit of normal
ULOQ	Upper limit of quantitation
VE	Vaccine Efficacy
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods and data handlings to be employed for the analysis of the study protocol 2126U0232, Amendment 3, dated 8 July 2022. Table, figure, and listing (TFL) mock-ups are provided in the TFL shells prepared separately.

All the analyses described in the SAP will be performed in the [redacted]. Any deviations from the SAP will be documented in the clinical study report.

2. OVERVIEW

This study is a multicenter, randomized, observer-blind, placebo-controlled, cross-over phase 3 study to evaluate the efficacy, safety and immunogenicity of S-268019-b in participants ≥ 18 years of age. Eligible participants will be randomly assigned to either the S-268019-b-preceding-vaccination group or the placebo-preceding-vaccination group in a 2:1 ratio.

The randomization will be stratified by age group (18 to 64 years and ≥ 65 years). Participants will receive either S-268019-b or placebo on Day 1 and Day 29.

Following approximately six-month follow-up from the second vaccination given during the Initial Vaccination Period, participants will be scheduled for administration of 2 injections of the alternate intervention (blinded crossover, Day 225 and Day 253) in the Crossover Vaccination Period.

3. STUDY OBJECTIVES

3.1 Primary Objective

- To assess the efficacy of a 2-dose regimen of S-268019-b for the prevention of COVID-19 in the Initial Vaccination Period prior to crossover in participants without evidence of infection before vaccination as compared to placebo.

3.2 Key Secondary Objective

- To assess the efficacy of S-268019-b for the prevention of symptomatic infection of COVID-19 as compared to placebo.

3.3 Secondary Objective

- To assess the efficacy of S-268019-b for the prevention of symptomatic infection of COVID-19 as compared to placebo.

- To assess the efficacy of a 2-dose regimen of S-268019-b for the prevention of asymptomatic infection of COVID-19 in participants without evidence of infection before vaccination.

- To assess the safety and reactogenicity of S-268019-b.

- To assess the immunogenicity of a 2-dose regimen of S-268019-b in the subset of immunogenicity subset.

3.4 Exploratory Objective

- To assess the durability of VE in the Crossover Vaccination Period.
- To explore SARS-CoV-2 genetic variants in participants diagnosed with COVID-19.

4. STUDY DESIGN

4.1 Study Blinding and Randomization

This is an observer-blind study and study intervention is blinded to the participants, investigators, subinvestigators, site staff who are not involved in preparation and administration of the study intervention. The sponsor, and the sponsor's designees involved in blinded monitoring, data management, or other aspects of the study will be kept blinded to the allocation of the active-control and S-268019-b. The Independent Data Monitoring Committee, unblinded staff involved in the assessment of safety, and unblinded clinical monitors will be unblind. Also, the site pharmacist or qualified designee who will prepare the solution will be unblinded so that he/she may obtain the assigned study intervention and prepare the dosing solutions.

All participants will be centrally assigned to randomized study intervention using an IWRS. The randomization will be stratified by age group (18 to 64 years of age and ≥ 65 years of age). Before the study is initiated, the login information and directions for the IWRS will be provided to each site.

Study intervention will be dispensed at the study visits summarized in the Schedule of Activities (SoA, Appendix 2, Appendix 3). The IWRS will be responsible for the allocation of randomization numbers to individual participants. Randomization will take place on Day 1 in the Initial Vaccination Period after the investigator confirms that a participant is eligible for the study. Participants will be randomized to either the S-268019-b-preceding group or the placebo-preceding group in a 2:1 ratio. At the time of blinded crossover (Day 225), the IWRS system will assign participants to the alternative treatment from that which they received in the Initial Vaccination Period.

Table 1 Intervention Groups

Group	Sample size	Intervention in the Initial Vaccination Period		Intervention in the Crossover Vaccination Period	
		Day 1	Day 29	Day 225	Day 253
S-268019-b-preceding group	36,610	S-268019-b 0.5 mL		Placebo 0.5 mL	
Placebo-preceding group	18,305	Placebo 0.5 mL		S-268019-b 0.5 mL	

4.2 Sample Size

Approximately 54,915 participants will be randomized in a 2:1 ratio to 2 IM doses of either S-268019-b (the S-268019-b-preceding group, n = approximately 36,610) or saline placebo (the placebo-preceding group, n = approximately 18,305) 4 weeks apart, on Days 1 and 29.

For the primary efficacy analysis, a total of 66 participants meeting the primary efficacy endpoint definition within the population of participants who are seronegative and PCR-negative at baseline and have not met the criteria for the primary efficacy endpoint prior to 14 days post second vaccination are required to demonstrate with at least 90% power that a VE is above 30%, assuming a VE of 70%, with unblinded interim analyses for early efficacy stopping at 50% and 75% of the target total number of participants meeting the primary efficacy endpoint definition using an exact conditional test based on Poisson assumption with a 1-sided alpha level of 0.025 [14]. Approximately 54,915 participants will be randomized assuming an observed attack rate of 0.5% per year in participants receiving placebo, 10% of the unevaluable participants due to dropout and/or baseline seropositive, and 6-month follow-up of each participants.

5. ANALYSIS POPULATIONS

The following analysis populations will be analyzed for this study based on enrolled participants with GCP compliance.

5.1 Enrolled

All participants who sign the ICF.

5.2 Randomized

All participants randomly assigned to study intervention.

5.3 Full Analysis Set (FAS)

This population will include all randomized participants who receive at least one dose of the study intervention in the Initial Vaccination Period. Participants in this population will be analyzed according to the treatment to which they were randomized.

5.4 Modified Intent to Treat (mITT) Population

This population will include participants in the FAS excluding participants who have evidence of past or present SARS-CoV-2 infection at baseline (ie, positive for RT-PCR or IgG antibody against SARS-CoV-2 N-protein). Participants in this population will be analyzed according to the treatment to which they were randomized.

5.5 Per Protocol Set (PPS)

This population will include all randomized participants who are included in the mITT Population and have no major protocol deviations in the Initial Vaccination Period. Participants in this population will be analyzed according to the treatment to

which they were randomized.

5.6 Crossover Subset

This population will include all randomized participants who are included in the mITT Population and receive at least one dose of the study intervention after crossover excluding participants who have met the criteria for the primary efficacy endpoint in the Initial Vaccination Period. Participants in this population will be analyzed according to the treatment to which they were randomized.

5.7 Immunogenicity Subset

This population will include the participants selected from all randomized participants who are included in the mITT Population and have a valid immunogenicity test result prior to the first dose of vaccination and at least 1 valid result after the first dose of vaccination. Participants in this population will be analyzed according to the intervention that they actually received.

5.8 Safety Analysis Set

This population will include randomized participants who received at least one dose of study intervention. Participants in this population will be analyzed according to the intervention that they actually received.

6. STATISTICAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1 Statistical Reporting

In general, continuous variables will be summarized by using the number of non-missing observations, arithmetic mean, standard deviation (SD), median, minimum, and maximum values as summary statistics; categorical variables will be summarized by using the frequency count and the percentage of participants in each category. Individual participant data and any derived data will be presented by participant.

All analyses will be performed using SAS® Version 9.4 or higher (SAS Institute, Cary, NC, USA).

6.2 Statistical Testing

All statistical tests will be performed at the two-sided significance level of 0.05, unless otherwise noted. No multiplicity adjustment will be made except interim analyses in this study.

6.3 Analysis Visit Windows

Analysis visit windows shown in Table 3 will be used to determine the analysis value for a particular study visit or time point. Measurements collected outside of the analysis visit window will be excluded from the by-visit analysis. For all participants with multiple measurements within an analysis visit window, the measurement obtained closest to the target study day will be used for the analysis. The target study day of Analysis Time Point of Day 29 will be defined referring to the date of initial

dose of the study intervention as Day 1, and the target study day of Analysis Time Point from Day 57 to Day 225 will be defined referring to the date of second dose of the study intervention as Day 29. In addition, the target study day of Analysis Time Point of Day 253 and Day 435 will be defined referring to the date of third dose of the study intervention as Day 225 and the date of Visit 6 as Day 253, respectively. If there are multiple measurements equidistant to the target study day, the earliest measurements will be used.

Table 3 Analysis Visit Windows

Analysis Time Point	Target Study Day	Analysis Visit Window
Baseline	1	Prior to the first dose of study intervention
Day 29	29	±3 days
Day 57	28 days after Visit 2	±7 days
Day 97	68 days after Visit 2	±14 days
Day 225	196 days after Visit 2	±14 days*
Day 253	28 days after Visit 5	±3 days
Day 435	182 days after Visit 6	±14 days

*: Immunogenicity data should be prior to the study intervention at Day 225.

6.4 Missing Data

Missing values will not be imputed. All statistical analyses will be based on observed cases unless otherwise noted.

6.5 Definition

6.5.1 Study Day

Study Day 1 will refer to the date of initial dose of the study intervention. Study days are defined relative to Study Day 1. Previous day to Study Day 1 is expressed as Day -1 (there is no Study Day 0).

In addition, day relative to vaccination will be derived for each vaccination dose.

6.5.2 Baseline

Baseline in the initial vaccination period will be defined as the last value obtained before first dose of intervention.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1 Participant Disposition

The number of participants who failed the Screening Period (ie, screen failure) will be summarized along with the reason for not being randomized to intervention/not treated with the study intervention.

A summary table will be produced detailing the number of participants randomized, the number of participants who completed the study, and the number of participants

who prematurely discontinued from the study. In addition, the reason for discontinuation from the study will be summarized.

The number and proportion of participants in each analysis population will be summarized, as well as the reasons for exclusion from the FAS, the mITT, the PPS, the Crossover Subset, the Immunogenicity Subset, and the Safety Analysis population.

7.2 Demographic and Baseline Characteristics

Demographic data and baseline characteristics shown in Table 4 will be summarized descriptively as described in Section 6.1 for the FAS, the mITT, and the Safety Analysis population. The summary table for the Safety Analysis population will also be produced for participants who received the study intervention in the Crossover Vaccination Period. The categories used to summarize the items are shown in Table 4.

Table 4 Demographic and Baseline Characteristics

Continuous variables	• Age • Height • Weight • BMI
Categorical variables	• Age (<30, ≥30 to <40, ≥40 to <50, ≥50 to <60, ≥60 to <65, ≥65) * • Sex (“Male”, “Female”) • Race (“American Indian or Alaska Native”, “Asian”, “Black or African American”, “Native Hawaiian or Other Pacific Islander”, “White”, “Not Reported”, “Unknown”) • Ethnicity (“Not Hispanic or Latino”, “Hispanic or Latino”, “Not reported”, “Unknown”) • Habits of smoking (“Yes”, “No”) • Baseline results of anti-SARS-CoV-2 N-protein antibody test (“Positive”, “Negative”)**

*: Only for table
**: For summary table for participants who received the study intervention in the Crossover Vaccination Period, the last value obtained before the corresponding intervention will be used.

Medical histories will be summarized for the Safety Analysis population. The reported medical history terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1.

7.3 Protocol Deviation

For all randomized participants, the number of participants with any important protocol deviation and the number of participants with important protocol deviation by category of important protocol deviation defined in protocol deviation plan will be

summarized. Participants who have the important protocol deviation more than once in different categories will be counted once by each category.

For all randomized participants, important protocol deviation will be presented in a listing.

8. STUDY CONDUCT

8.1 Intervention Exposure and Compliance

For the Safety Analysis population, the number of doses of study intervention administered to participants will be summarized descriptively by intervention group and by intervention period.

8.2 Prior and Concomitant Drugs and Therapies

Prior and concomitant drugs will be coded using the World Health Organization (WHO) Drug Dictionary (B3 Format Seq 1, 2021). Prior drugs and therapies will be defined as medication taken prior to Day 1. Concomitant drugs and therapies will be defined as medication taken on or after Day 1.

For the Safety Analysis population, the number and proportion of participants who took prior and concomitant drugs will be summarized by WHO Drug Dictionary Preferred Term (PT) by intervention group. If a participant has more than one drug that codes to the same PT, the participant will be counted only once for that PT.

The number and proportion of participants who took prior and concomitant therapies will be summarized by the reported therapy name for the Safety Analysis population by intervention group. Participants for whom a particular therapy was reported more than once will be counted only once for that therapy.

9. EFFICACY ENDPOINT

The primary efficacy analysis and analyses for (key) secondary efficacy endpoints will be performed based on the data generated in the Initial Vaccination Period.

9.1 Primary Endpoint

The primary endpoint will be the first occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 in the Initial Vaccination Period (ie, prior to crossover), with onset at least 14 days following the second vaccination in participants seronegative and PCR-negative at baseline.

The primary endpoint will be analyzed on the mITT Population and supported by analysis of the PPS.

Participants will be censored at the time of last date of study participation in the Initial Vaccination Period, efficacy data cutoff date, administration of the approved vaccine, or the last date of symptomatic COVID-19 evaluation in the Initial Vaccination Period, whichever is earlier. The last date of symptomatic COVID-19 evaluation in

the Initial Vaccination Period is defined as the earlier date of the previous day of the crossover vaccination at Visit 5, and the day after 195 days of Visit 2.

9.1.1 Primary Analysis

As the primary efficacy analysis, the plan is to use a Poisson regression model with robust error variance [1] to analyze the primary endpoint, which will include the intervention group, baseline age (continuous) as factors as well as the log of the follow-up time as an offset. The Vaccine Efficacy (VE) will be estimated from the model, which will give the relative risk (RR) in the incidence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 occurring during approximate six months (ie, from 14 days post second vaccination in the Initial Vaccination Period to the third vaccination in the Crossover Vaccination Period). The following is a sample of SAS code used to estimate the RR:

```
proc genmod data=AnalysisData;
  class subjid trtp(ref='0') / param=ref;
  model y=trtp age / dist=poisson link=log offset=log_time;
  repeated subject=subjid / type=unstr;
  estimate 'RR' trtp 1 / exp;
run;
```

- subjid: the participant identifier
- trtp: the allocated treatment group (S-268019-b-preceding group: 1, placebo-preceding group: 0)
- y: whether a participant met the primary endpoint or not (participant who met the primary endpoint: 1, participant who did not met the primary endpoint: 0)
- log_time: the natural log of the follow-up time
- age: age at the time of informed consent

VE is calculated as 1 minus the relative risk of the primary endpoint among the S-268019-b-preceding group (S-268019-b) versus the placebo-preceding group (placebo). A two-sided 95% confidence interval (CI) for VE will be constructed. If the Poisson regression model with robust error variance fails to converge, an alternative approach will be implemented.

The efficacy will be demonstrated if the null hypothesis VE ≤ 30% is rejected at the alpha level adjusted hypothesis test at each analysis, that is, when the lower limit of CI for VE > 30%.

9.1.2 Secondary Analysis

The number of cases, the incidence rate and its 95% CI will be calculated by intervention group. The incidence rate will be calculated as the number of participants with an event divided by the total person-years at risk. The 95% CI of the incidence rate will be calculated using the exact method assuming Poisson distribution of events.

Cumulative incidence rates of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 occurring in the Initial Vaccination Period will be estimated with the Kaplan-Meier method.

9.1.3 Supplementary Analysis

- The above primary and secondary analyses will be repeated in the PPS.

9.1.4 Subgroup Analysis

The primary endpoint will be analyzed to estimate the VE and its 95% CI using the similar model by the following subgroups.

- Age group (18 to 64 years or ≥ 65 years)

9.2 Secondary Endpoints

The secondary efficacy endpoints for the evaluation in the participants seronegative and PCR-negative at baseline will be analyzed on the mITT, and those for the evaluation in the participants regardless of serostatus or PCR status at baseline will be analyzed on the FAS.

The (key) secondary efficacy endpoints will be analyzed using the same manner as the primary and secondary efficacy analyses. The analysis of the (key) secondary endpoint will be performed using an unadjusted alpha level.

The key secondary endpoints are:

- The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 in the Initial Vaccination Period with onset at least 14 days following the second vaccination in participants seronegative and PCR-negative at baseline.

- The first occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 in the Initial Vaccination Period in participants seronegative and PCR-negative at baseline.

- The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 in the Initial Vaccination Period in participants seronegative and PCR-negative at baseline.

The other secondary endpoints are:

- The first occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 in the Initial Vaccination Period with onset at least 14 days following the second vaccination in participants regardless of serostatus or PCR status at baseline.

- The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 in the Initial Vaccination Period with onset at least 14 days following the second vaccination in participants regardless of serostatus or PCR status at baseline.

- The first occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 in the Initial Vaccination Period in participants regardless of serostatus or PCR status at baseline.

- The first occurrence of SARS-CoV-2 RT-PCR-positive severe COVID-19 in the Initial Vaccination Period in participants regardless of serostatus or PCR status at baseline.

- The first occurrence of asymptomatic SARS-CoV-2 infection in the Initial Vaccination Period beginning 14 days following the second vaccination in participants seronegative and PCR-negative at baseline. Antibodies to SARS-CoV-2 N-protein will be used to determine natural infection and to determine the incidence of asymptomatic infection acquired during study follow-up. Participants will be censored at the time of last date of study participation in the Initial Vaccination Period, efficacy data cutoff date, first symptomatic COVID-19, administration of the approved vaccine, or the last date of asymptomatic COVID-19 evaluation in the Initial Vaccination Period, whichever is earlier. The last date of asymptomatic COVID-19 evaluation in the Initial Vaccination Period is defined as the earlier date of the crossover vaccination at Visit 5, and the day after 196 days of Visit 2.

9.3 IMMUNOGENICITY ENDPOINT

Immunogenicity analyses will be performed for the Immunogenicity Subset.

For immunogenicity variables, data inferior to the lower limit of quantification (LLOQ) will be replaced by the half the detection limit. Titer values measured as above the upper limit of quantification (ULOQ) will be imputed at the ULOQ value.

Immunogenicity data obtained after a postbaseline dose of approved vaccine, a postbaseline positive anti N protein antibody or SARS-CoV-2 RT-PCR test result, or a postbaseline onset of COVID-19 will not be included in the analysis.

9.3.1 GMT of SARS-CoV-2 Neutralizing Antibody at Each Time Point

The GMT will be calculated by taking the back transformation of the arithmetic mean of the log-transformed titers.

9.3.1.1 Analysis

For SARS-CoV-2 neutralizing antibody at each time point, the GMT and the corresponding two-sided 95% confidence interval (CI) will be calculated for each intervention group by back transformation of the arithmetic mean and its CIs of the log-transformed titers. The 95% CI in log-transformed titers will be constructed using Student's *t* distribution. The GMT ratios between intervention groups with the corresponding 95% CI will be estimated by back transformation of the intervention difference and its 95% CI which are obtained using analysis of covariance (ANCOVA) model fitted on the log-transformed titers. Comparisons between intervention groups will be made using the same model. The model will include intervention group as fixed effect as well as age (continuous) as a covariate.

A box and whisker plot will be created by intervention group, and time point.

9.3.2 Geometric Mean Fold Rise (GMFR) of SARS-CoV-2 Neutralizing Antibody at Each Time Point

The calculation for GMFR will be performed by taking the back transformation of the arithmetic mean of the change from baseline in log-transformed titers, where

Change from baseline = (log titer at each time point) – (log titer at baseline)

9.3.2.1 Analysis

For SARS-CoV-2 neutralizing antibody at each time point, the GMFR and the corresponding two-sided 95% confidence interval (CI) will be calculated for each intervention group by back transformation of the arithmetic mean and its CIs of the change from baseline in log-transformed titers. The 95% CI in log-transformed titers will be constructed using Student's *t* distribution.

9.3.3 SARS-CoV-2 Neutralizing Antibody Seroconversion at Each Time Point

The definition of SARS-CoV-2 neutralizing antibody seroconversion will be at least four-fold increase from baseline in SARS-CoV-2 neutralizing antibody titer.

9.3.3.1 Analysis

For SARS-CoV-2 neutralizing antibody seroconversion at each time point, the proportion of seroconversion and the corresponding 95% CI will be estimated for each intervention group. The 95% CI will be calculated using the Clopper-Pearson method. The difference between intervention groups and the corresponding 95% CI will be also estimated.

9.3.4 GMT of Anti-spike Protein IgG at Each Time Point

The GMT will be calculated in the same way as Section 9.3.1.

9.3.4.1 Analysis

The GMT of anti-spike protein IgG at each time point will be analyzed in the same way as Section 9.3.1.1.

9.3.5 GMFR of Anti-spike Protein IgG at Each Time Point

The GMFR will be calculated in the same way as Section 9.3.2.

9.3.5.1 Analysis

The GMFR of anti-spike protein IgG at each time point will be analyzed in the same way as Section 9.3.2.1.

9.3.6 Anti-spike Protein IgG Seroconversion at Each Time Point

The anti-spike protein IgG seroconversion will be defined in the same way as Section 9.3.3.

9.3.6.1 Analysis

The anti-spike protein IgG seroconversion at each time point will be analyzed in the same way as Section 9.3.3.1.

10. EXPLORATORY ENDPOINTS

10.1 Durability of Vaccine Efficacy

Durability of vaccine efficacy will be assessed by the summarizing for exploratory efficacy endpoints generated in the Crossover Vaccination Period.

The endpoints are:

- The first occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 with onset at least 14 days following the second vaccination in the Crossover Vaccination Period.

- The first occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 in the Crossover Vaccination Period.

- The first occurrence of asymptomatic SARS-CoV-2 infection beginning 14 days following the second vaccination in the Crossover Vaccination Period.

- The first occurrence of asymptomatic SARS-CoV-2 infection in the Crossover Vaccination Period.

  Antibodies to SARS-CoV-2 N-protein will be used to determine natural infection and to determine the incidence of asymptomatic infection acquired during study follow-up.

10.1.1 Analysis

- The number of cases, the incidence rate and its 95% CI will be calculated by intervention group. The incidence rate will be calculated as the number of participants with an event divided by the total person-years at risk. The 95% CI of the incidence rate will be calculated using the exact method assuming Poisson distribution of events.

- The post-crossover VE with 95% CI will be estimated as VE2=100×(1-RR1×RR2), where RRk is the relative risk of incidence rates for the S-268019-b-preceding group versus the placebo-preceding group in period k (period 1: Initial Vaccination Period, period 2: Crossover Vaccination Period). Each relative risk will be estimated using a Poisson regression model with robust error variance, which will treat the data across the two periods as independent and include the intervention group (S-268019-b-preceding group, Placebo-preceding group), the period identifier (period 1, period 2), the interaction between the intervention group and the period identifier, baseline age (continuous) as factors as well as the log of the follow-up time of each period as an offset [2]. The analysis will be based on pooled data of the first occurrence of symptomatic/asymptomatic COVID-19 with onset at least 14 days following the second vaccination in the Initial Vaccination Period in the mITT Population, and the first occurrence of symptomatic/asymptomatic COVID-19 in the Crossover Vaccination Period of S-268019-b-preceding group and the first occurrence of symptomatic/asymptomatic with onset at least 14 days following the second vaccination in the Crossover Vaccination Period of Placebo-preceding group in the Crossover Subset. The

following is a sample of SAS code used to estimate the RR1×RR2:

```
proc genmod data=AnalysisData;
  class id trtp(ref='0') period(ref='1') / param=ref;
  model y=trtp period trtp*period age / link=log
  dist=poisson offset=log_time;
  repeated subject=id / type=unstr;
  estimate 'RR1*RR2' trtp 2 trtp*period 1 / exp;
run;
```

- id: the identifier for each observation
- trtp: the allocated treatment group (S-268019-b-preceding group: 1, placebo-preceding group: 0)
- period: the period identifier (period 1: 1, period 2: 2)
- y: whether a participant met the endpoint or not (participant who met the endpoint: 1, participant who did not met the endpoint: 0)
- log_time: the natural log of the follow-up time
- age: age at the time of informed consent

10.2 Nucleotide Sequences of SARS-CoV-2 Viral Genomes

For participants who are tested positive for SARS-CoV-2 with onset of COVID-19, the genome of SARS-CoV-2 virus strain will be listed.

11. SAFETY

All safety analyses will be performed for the Safety Analysis population by intervention period unless otherwise specified.

11.1 Adverse Events

Adverse events (AEs) will be coded and classified by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1. Unless otherwise specified, analyses will be based on treatment-emergent adverse events (TEAEs), which is any AE reported after the initial dose of the study intervention.

The number and proportion of participants who experienced at least one AE will be summarized by intervention group. The proportions will be presented along with its 95% CIs, calculated with the Clopper-Pearson method. The number of events reported will also be calculated. The following items will be summarized in the same manner.

(1) AEs with an outcome of death, other serious adverse events (SAEs), medically attended adverse events (MAAEs), AEs of special interest (AESIs), and AEs leading to discontinuation of the study intervention

(2) Treatment-related AEs, treatment-related AEs with an outcome of death, nonfatal treatment-related SAEs, treatment-related MAAEs, treatment-related AESIs, and treatment-related AEs leading to discontinuation of the study intervention

The definitions of these events are shown in Table 5.

Table 5 Definition of Adverse Event Terms

Term	Definition
AE with an outcome of death	AE with "Fatal" in terms of outcome
Other SAE	SAE excluding an AE with an outcome of death
AE leading to discontinuation of the study intervention	AE with "Drug withdrawn" in terms of the action taken with study drug
Treatment-related AE	AE with "Related" in terms of the causal relationship to study drug

AE = adverse event; SAE = serious adverse event

The definitions of AESIs are shown in Table 6.

Table 6 Definition of Adverse Event of Special Interest

Neuroinflammatory disorders	**Musculoskeletal disorders**	**Skin disorders**
• Cranial nerve neuropathy, including paralysis and paresis (eg, Bell's palsy). • Optic neuritis. • Multiple sclerosis. • Transverse myelitis. • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants. • Acute disseminated encephalomyelitis, including site specific variants, eg, noninfectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis. • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome. • Demyelinating peripheral neuropathies including: - Chronic inflammatory demyelinating polyneuropathy. - Multifocal motor neuropathy. - Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy.	• Systemic lupus erythematosus and associated conditions. • Systemic scleroderma (systemic sclerosis), including: - Diffuse scleroderma. - CREST syndrome. • Idiopathic inflammatory myopathies, including: - Dermatomyositis. - Polymyositis. • Anti-synthetase syndrome. • Rheumatoid arthritis and associated conditions including: - Juvenile idiopathic arthritis. - Still's disease. • Polymyalgia rheumatica. • Spondyloarthropathies, including: - Ankylosing spondylitis. - Reactive arthritis (Reiter's syndrome). - Undifferentiated spondyloarthritis. - Psoriatic arthritis. - Enteropathic arthritis. • Relapsing polychondritis. • Mixed connective tissue disorder. • Gout.	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid, and dermatitis herpetiformis). • Lichen planus. • Sweet's syndrome. • Localized scleroderma (morphea).
Liver disorders	**Gastrointestinal disorders**	**Endocrine disorders**
• Autoimmune hepatitis. • Primary biliary cirrhosis. • Primary sclerosing cholangitis. • Autoimmune cholangitis. -	• Inflammatory bowel disease, including: - Crohn's disease. - Ulcerative colitis. - Microscopic colitis. - Ulcerative proctitis. • Celiac disease. • Autoimmune pancreatitis.	• Autoimmune thyroiditis (Hashimoto thyroiditis). • Grave's or Basedow's disease. • Diabetes mellitus type 1. • Addison's disease. • Polyglandular autoimmune syndrome. • Autoimmune hypophysitis.
Vasculitis	**Blood disorders**	**Others**
• Large vessels vasculitis including:	• Autoimmune hemolytic anemia.	• Autoimmune glomerulonephritis including:

- Giant cell arteritis (temporal arteritis). - Takayasu's arteritis. • Medium sized and/or small vessels vasculitis including: - Polyarteritis nodosa. - Kawasaki's disease. - Microscopic polyangiitis. - Wegener's granulomatosis (granulomatosis with polyangiitis). - Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis). - Buerger's disease (thromboangiitis obliterans). - Necrotizing vasculitis (cutaneous or systemic). - Antineutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified). - Henoch-Schonlein purpura (IgA vasculitis). - Behcet's syndrome. - Leukocytoclastic vasculitis.	• Autoimmune thrombocytopenia. • Antiphospholipid syndrome. • Pernicious anemia. • Autoimmune aplastic anemia. • Autoimmune neutropenia. • Autoimmune pancytopenia.	- IgA nephropathy. - Glomerulonephritis rapidly progressive. - Membranous glomerulonephritis. - Membranoproliferative glomerulonephritis. - Mesangioproliferative glomerulonephritis. - Tubulointerstitial nephritis and uveitis syndrome. • Ocular autoimmune diseases including: - Autoimmune uveitis. - Autoimmune retinitis. • Autoimmune myocarditis. • Sarcoidosis. • Stevens-Johnson syndrome. • Sjögren's syndrome. • Alopecia areata. • Idiopathic pulmonary fibrosis. • Goodpasture syndrome. • Raynaud's phenomenon.

(3) Solicited systemic AEs, solicited local AEs, and unsolicited AEs

(4) Treatment-related solicited systemic AEs, treatment-related solicited local AEs, and treatment-related unsolicited AEs

Solicited systemic AEs, solicited local AEs, unsolicited AEs, and treatment-related solicited AEs are defined as shown in Table 7.

Table 7 Definition of Solicited Adverse Events

Systemic / local	Definition
Solicited systemic AEs	The solicited systemic AEs are defined as the AEs which occur within the first 7 days after each vaccination in Initial Vaccination Period and are grouped into one of the following AE names: • Fever • Nausea/vomiting

Systemic / local	Definition
	• Diarrhea • Headache • Fatigue • Myalgia
Solicited local AEs	The solicited local AEs are defined as the AEs which occur within the first 7 days after each vaccination in Initial Vaccination Period and are grouped into one of the following AE names: • Pain • Erythema/redness • Induration • Swelling
Unsolicited AEs	AEs other than solicited systemic or local AE

The number and proportion of participants who experience AEs will be summarized by SOC and PT for each intervention group. For these summaries, participants with multiple AEs will be counted only once within an SOC and PT. Treatment-related AEs, MAAEs, treatment-related MAAEs, AESIs, treatment-related AESIs, AEs leading to discontinuation of the study intervention, treatment-related AEs leading to discontinuation of the study intervention, unsolicited AEs, and treatment-related unsolicited AEs will be summarized in the same manner.

The number and proportion of participants who experience AEs in each category of severity, outcome and duration will be summarized by SOC and PT for each intervention group. Participants who experience the same AE more than once in different categories will be counted only once by the highest priority shown in Table 8 within a SOC and PT. The duration is calculated as (Date of AE outcome – Date of AE onset + 1) if the outcome is “Recovering/resolving” or “Recovered/resolved”, otherwise the duration is regarded as ≥29. Treatment-related AEs will be summarized in the same manner.

The number and proportion of participants who experience solicited systemic AEs in each category of severity will be summarized by the AE name (fever, nausea/vomiting, diarrhea, headache, fatigue, and myalgia) for each intervention group and dose of study intervention. Participants who experience the same solicited systemic AE more than once in different categories will be counted only once by the highest priority shown in Table 8 within an AE name. Solicited local AEs, treatment-related solicited systemic AEs, and treatment-related solicited local AEs will be summarized in the same manner.

Table 8 Priority of Categories

Priority	Category		
	Severity	Outcome	Duration (days)
1	Grade 5	Fatal	≥29
2	Grade 4	Recovered/resolved with sequelae	15 to 28
3	Grade 3	Not recovered/not resolved	8 to 14
4	Grade 2	Recovering/resolving	1 to 7
5	Grade 1	Recovered/resolved	
6		Unknown	

The number and proportion of participants who experience AEs in each category of timing of onset will be summarized by SOC and PT for each intervention group. The denominator for the percentage will be the number of participants who are assessed during each category period. If a participant experienced the same AE more than once in different categories, the participant will be counted once in each category. The time of onset categories includes 1 to 8 days, 9 to 15 days, 16 to 28 days, 29 to 36 days, 37 to 43 days, 44 to 56 days, and ≥57 days. The number of days to onset is calculated as (Date of AE onset – Date of first dose of the study intervention + 1).
Treatment-related AEs will be summarized in the same manner.

The number and proportion of participants who experience solicited systemic AEs in each category of onset will be summarized by the AE name (fever, nausea/vomiting, diarrhea, headache, fatigue, and myalgia) for each intervention group. The denominator for the percentage will be the number of participants who are exposed to the study intervention at each vaccination. If a participant experienced the same AE more than once in different categories, the participant will be counted once in each category. The time of onset categories includes 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, and 8 days after each vaccination. The median time of onset of solicited systemic AEs after each vaccination will be estimated by the AE name for each intervention group. The number of days to onset is calculated as (Date of AE onset – Date of dose of the study intervention + 1). Solicited local AEs, treatment-related solicited systemic AEs, and treatment-related solicited local AEs will be summarized in the same manner.

The number and proportion of participants who experience solicited systemic AEs in each category of duration after each vaccination will be summarized by the AE name (fever, nausea/vomiting, diarrhea, headache, fatigue, and myalgia) for each study intervention group. If a participant experienced the same AE more than once in different categories, the participant will be counted once in each category. The time of duration categories includes 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, and 8 or more days after onset. The median time of duration of solicited systemic AEs after each vaccination will be estimated by the AE name for each intervention group. The duration is calculated as (Date of AE outcome – Date of AE onset + 1) if the outcome is “Recovering/resolving” or “Recovered/resolved”, otherwise the duration is regarded as ≥8. Solicited local AEs, treatment-related solicited systemic AEs, and treatment-related solicited local AEs will be summarized in the same manner.

11.2 Vital Signs

Summary statistics for vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) will be calculated by intervention group for each time point, and those for the change from baseline will also be calculated by intervention group to each time point.

12. INTERIM ANALYSES

At first, two interim analyses were planned during the Initial Vaccination Period, but the total target cases are likely to be accumulated, so the sponsor decided not to conduct the interim analyses.

The primary analysis will be performed using the cut off data obtained after the total target cases are accumulated.

13. ANALYSES PRIOR TO STUDY COMPLETION

As the study progresses after the primary analysis with the first interim locked database, the analyses planned for the Initial Vaccination Period will be performed again based on available data from the second interim locked database to review efficacy, immunogenicity and safety.

14. PROGRAMMING CONVENTIONS

14.1 Formatting and Programming Rule

Unless otherwise noted, the following conventions should be used when constructing the analysis TFLs:

- Every summary table and figure should clearly specify the analysis population being summarized. Listings also should specify the analysis population being listed.
- Rounding for all variables will occur only as the last step, immediately prior to presentation in TFLs. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:
  - Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
  - Means, SDs, and medians will be reported to 1 decimal place beyond the number of decimal places with which the original endpoint is presented.
  - Minimums and maximums will be reported to the same number of significant digits as the raw measurements.
  - Calculated percentages will be reported to 1 decimal place.

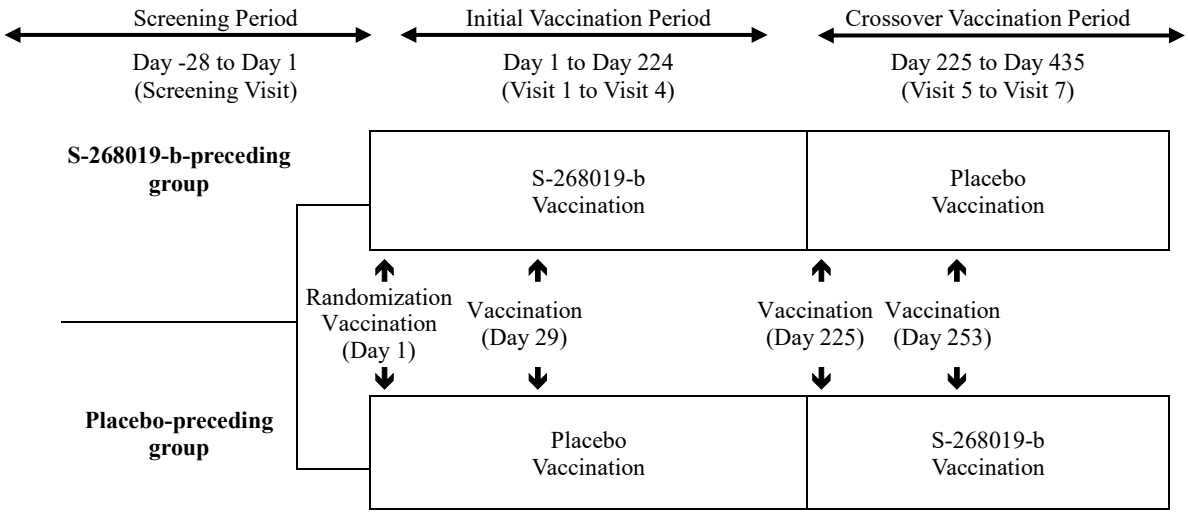
- All means presented will be arithmetic unless otherwise stated.

15. REFERENCES

[1] Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. Am J Epidemiol 2004;159(7):702-6.

[2] Follmann D, Fintzi J, Fay MP, Janes HE, Baden LR, El Sahly HM, Fleming TR, Mehrotra DV, Carpp LN, Juraska M, Benkeser D, Donnell D, Fong Y, Han S, Hirsch I, Huang Y, Huang Y, Hyrien O, Luedtke A, Carone M, Nason M, Vandebosch A, Zhou H, Cho I, Gabriel E, Kublin JG, Cohen MS, Corey L, Gilbert PB, Neuzil KM. A Deferred-Vaccination Design to Assess Durability of COVID-19 Vaccine Effect After the Placebo Group Is Vaccinated. Ann Intern Med. 2021 Aug;174(8):1118-1125.

Appendix 1 Study Schematic



If a participant has any of COVID-19-related symptoms during the study, he/she will visit the study site for the Potential COVID-19 Illness Visit.

Appendix 2 Schedule of Activities for Participants without COVID-19 (SoA)

Period		Screening Period	Initial Vaccination Period (Day 1 to Day 224)				Crossover Vaccination Period (Day 225 to Day 435)			Unscheduled
Visit		Screening [a]	1	2	3	4	5	6	7	
Day		-28 to 1	1	29 (Visit 1+28)	57 (Visit 2+28)	97 (Visit 2+68)	225 (Visit 2+196)	253 (Visit 5+28)	435[b] (Visit 6+182)	Discontinuation
Visit window (days)			0	±3	±7	±14	±14	±3	±14	+3[c]
Informed consent		X								
Inclusion and exclusion criteria		X								
Enrollment/Randomization		X	X							
Study intervention			X	X[d]			X[d]	X[d]		
Physical examination[e]		X	X[f]	X	X	X	X	X	X	X
Demographics[g]		X								
Height, weight, BMI		X								
Past and current medical conditions		X								
Vital signs		X	X[f]	X	X	X	X	X	X	X
Pregnancy test[h]		X	← (X) →				← (X) →			X
Nasopharyngeal swab sample	SARS-CoV-2 RT-PCR		X[i]							
Blood sampling for immunogenicity tests	Anti-SARS-CoV-2 N-protein antibodies		X[i]		X	X	X[i]	X[i]	X	X
	Anti-SARS-CoV-2 S-protein IgG antibodies[j]		X[i]	X[i]	X	X	X[i]		X	X
	SARS-CoV-2 NAb[j]		X[i]	X[i]	X	X	X[i]		X	X
e-Diary	COVID-19-related		←X→							X

Period		Screening Period	Initial Vaccination Period (Day 1 to Day 224)				Crossover Vaccination Period (Day 225 to Day 435)			Unscheduled
Visit		Screening [a]	1	2	3	4	5	6	7	Discontinuation
Day		-28 to 1	1	29 (Visit 1+28)	57 (Visit 2+28)	97 (Visit 2+68)	225 (Visit 2+196)	253 (Visit 5+28)	435[b] (Visit 6+182)	
Visit window (days)			0	±3	±7	±14	±14	±3	±14	+3[c]
	symptoms[k]									
	Solicited AE (reported by participants)[l]		←X[l]→							
AE review[m]		X	←X→				←X→			X
SAE, MAAE, AESI review		X	←X→							X
Prior/Concomitant medication		X	←X[n]→							X

AE = adverse event; AESI = adverse events of special interest; BMI = body mass index; COVID-19 = coronavirus disease 2019; IgG = immunoglobulin G; MAAE = Medically Attended Adverse Event; N-protein = nucleocapsid protein; NAb = neutralizing antibody; RT-PCR = reverse transcription polymerase chain reaction; S-protein = SARS-CoV-2 spike glycoprotein; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; W = week; M = month, V = visit; Vax = visit for vaccination

a) Can be conducted on the same day as Day 1.
b) 6 months after 4th Vax.
c) Within 3 days from decision to discontinue the study.
d) Vaccination should be done within the visit window whenever possible, but it may be postponed for the reasons described in Clinical Study Protocol, Section 6.2.3.
e) A complete physical examination will be performed at screening followed by brief physical examinations.
f) Assessed before vaccination. Need not to repeat in participants who are screened on Day 1.
g) Including year of birth, age at the time of signing the informed consent form, sex, ethnicity, race, smoking status, medical history.
h) Only for women of childbearing potential (WOCBP). The pregnancy test (urine or serum as required by local regulations) will be performed at screening and also when it is deemed necessary by the investigator or subinvestigator in the first 57 days of each period.
i) Nasopharyngeal swab and blood samples will be collected before vaccination.
j) Blood samples for anti-SARS-CoV-2 S-protein IgG antibodies and SARS-CoV-2 neutralizing antibodies will be collected from at least 650 participants (Clinical Study Protocol, Section 8.10).
k) Participants will complete surveillance for COVID-19-related symptoms at least once a week or whenever participants experience any new or worsened COVID-19-related symptoms.
l) Solicited local and systemic AEs and body temperatures are recorded during the 7-day periods after the vaccinations (Day 1 to 8 and Day 29 to 36).
m) AEs will be collected from the date of signing of the ICF to 4 weeks after the second vaccination (Initial Vaccination Period), and from the third vaccination to 4 weeks after the fourth vaccination (Crossover Vaccination Period).
n) During Day 58 to 224 and Day 254 to 435, only concomitant medication for treatment of SAE, MAAE, or AESI, or prohibited medication will be collected.

Appendix 3 Schedule of Activities for Participants with Suspected/Confirmed COVID-19 (COVID-19 Illness Visits)

Visit		Potential COVID-19 Illness Visit	(COVID-19 Illness Visit)*	COVID-19 Follow-up Visit[g]
Days		1[a]	Unscheduled	29 ± 3[b]
Physical examination		X	(X)	X
COVID-19 assessment				X[c]
Vital signs, SpO_2		X	(X)	X
Chest X-ray/CT or blood gas analysis[d]		← (X) →		
Pregnancy test[e]		← (X) →		
Nasopharyngeal swab sample	SARS-CoV-2 RT-PCR	X		
	Virus genome sequencing	X		
Blood collection for the immunogenicity tests	Anti-SARS-CoV-2 N-protein antibodies	X		
	Anti-SARS-CoV-2 S-protein IgG antibodies	X		X
	SARS-CoV-2 NAb	X		X
e-Diary	COVID-19-related symptoms[f]	←X→		
AE review		←X→		
SAE, MAAE, AESI review		←X→		
Concomitant medication		←X→		

AE = adverse event; AESI = adverse events of special interest; COVID-19 = coronavirus disease 2019; CT = computed tomography; IgG = immunoglobulin G; MAAE = Medically Attended Adverse Event, N-protein = nucleocapsid protein; NAb = neutralizing antibody; RT-PCR = real-time polymerase chain reaction; S-protein = SARS-CoV-2 spike glycoprotein; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = peripheral capillary oxygen saturation

a) Within 3 days from the date when the investigator or designee instructs a participant to visit the site. The Potential COVID-19 Illness Visit may be conducted as an in-person visit or telehealth visit. In the case of telehealth visit, a qualified site staff will visit participant's home or place of sojourn.
b) The COVID-19 Follow-up Visit will occur only for participants with a positive RT-PCR result.
c) Evaluate and record the severity of COVID-19, all the presented COVID-19 symptoms (including symptom onset date if there are any symptoms), and the presence or absence of RT-PCR tests outside the clinical trial sites (test results if performed).
d) To be performed for participants with respiratory symptoms at the discretion of the investigator.
e) Only for women of childbearing potential (WOCBP). The pregnancy test (urine or serum as required by local regulations) will be performed when it is deemed necessary by the investigator or subinvestigator.
f) Participants will evaluate COVID-19-related symptoms daily until all symptoms have disappeared.

g) If any COVID-19-related symptoms persist at the time of the COVID-19 Follow-up Visit, the investigator should continue the follow-up until the participant has fully recovered or been medically stable.

* COVID-19 Illness Visit(s) will be scheduled when the investigator judges participant's visit and additional examinations such as physical examination, vital signs, SpO_2, blood gas analysis, or chest X-ray/CT are necessary to manage COVID-19. If such examinations are performed, the results will be recorded in eCRF. Participants who have RT-PCR-positive SARS-CoV-2 infection will be monitored until they clinically recover (and if requested by local regulations, have negative RT-PCR results on two sequential samples taken at least 24 hours apart). Participants who are negative for SARS-CoV-2 RT-PCR will return to their respective study schedule. The COVID-19 Illness Visit may be conducted as an in-person visit or telehealth visit. In the case of telehealth visit, a qualified site staff will visit participant's home or place of sojourn.

Signature Page for [redacted]

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 26-Sep-2023 01:20:28 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 26-Sep-2023 01:26:42 GMT+0000

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