CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol 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
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1.1 Synopsis

Protocol 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

Protocol Number: 2126U0232

Compound Number: S-268019

Short Title: A Phase 3 Study of S-268019 for the Prevention of COVID-19

Rationale: This study will assess the efficacy, safety and immunogenicity of S-268019-b, a candidate prophylactic vaccine for the prevention of coronavirus disease 2019 (COVID-19). This study is planned to use the dose at which immunogenicity and safety were confirmed in the ongoing Phase 1/2 double-blind study of S-268019-b (2026U0221).

Objectives and Endpoints: The study objectives and endpoints are shown in Table 1-1.

Table 1-1 Objectives, Estimands and Endpoints

Objectives	Estimands/Endpoints
Primary	
● 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.	**Population:** Modified Intent to Treat (mITT) Population
	Endpoint: The first occurrence of SARS-CoV-2 reverse transcription polymerase chain reaction (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.
	Intercurrent events: For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint, the absence of data following these participants' withdrawal will be treated as missing; participants who withdrew before 14 days post second vaccination or who were diagnosed with SARS-CoV-2 infection prior to 14 days post second vaccination in the Initial Vaccination Period will be excluded from the primary endpoint analysis.
	Summary measure: Vaccine efficacy (VE), calculated as 1-relative risk. (Relative risk is the incidence of infection in the intervention group relative to the incidence of infection in the control group.)

Objectives	Estimands/Endpoints
Key Secondary	
● To assess the efficacy of S-268019-b for the prevention of symptomatic infection of COVID-19 as compared to placebo.	● 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.
Secondary	
● To assess the efficacy of S-268019-b for the prevention of symptomatic infection of COVID-19 as compared to placebo.	● 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.
● 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.	● 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.
● To assess the safety and reactogenicity of S-268019-b.	● The incidence of AEs, treatment-related AEs, SAEs, AESIs, MAAEs, solicited local AEs, and solicited systemic AEs, and vital signs in the Initial Vaccination Period and the Crossover Vaccination Period.
● To assess the immunogenicity of a 2-dose regimen of S-268019-b in the subset of immunogenicity subset.	● The following items for SARS-CoV-2 neutralizing antibody titer and anti-SARS-CoV-2 S-protein

Objectives	Estimands/Endpoints
	immunoglobulin G (IgG) antibody titers from Immunogenicity subset: – Geometric mean titer (GMT) – Geometric mean of fold rise of antibody titer (GMFR) – Seroconversion rate
Exploratory	
● To assess the durability of VE 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 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.
● To explore SARS-CoV-2 genetic variants in participants diagnosed with COVID-19.	● Nucleotide sequences of SARS-CoV-2 viral genomes detected in nasopharyngeal swabs from RT-PCR-positive participants analyzed with next-generation sequencing.

Overall Design:

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. A schematic overview of the study is presented in Figure 1-1.

Number of Participants:

54,915 participants (36,610 participants in the S-268019-b-preceding group, 18,305 participants in the placebo-preceding group).

Intervention Groups and Duration:

The study will be composed of a Screening Period (Day −28 to Day 1), an Initial Vaccination Period (Day 1 to Day 224), and a Crossover Vaccination Period (Day 225 to Day 435).

In the Initial Vaccination Period, the efficacy of a 2-dose regimen of S-268019-b against COVID-19 will be assessed compared to placebo. Participants will be randomly assigned

to the S-268019-b-preceding group or the placebo-preceding group in a 2:1 randomization ratio. Participants assigned to the S-268019-b-preceding group will receive S-268019-b and participants assigned to the placebo-preceding group will receive placebo. In the Crossover Vaccination Period, participants in the S-268019-b-preceding group will receive placebo and participants in the placebo-preceding group will receive S-268019-b. All participants who remain in the study at the time of the blinded crossover will be eligible for crossover vaccination, except for participants who have experienced an RT-PCR-positive COVID-19. The dose of the study intervention is shown in Table 1-2.

Participants will visit the study site on Days 1, 29, 57, 97, 225, 253 and 435, and receive a single-dose of study intervention by intramuscular injection on Day 1 and Day 29 in the Initial Vaccination Period, and on Day 225 and Day 253 in the Crossover Vaccination Period (Table 1-3).

If a participant reports any COVID-19-related symptoms (Table 8-1), the investigator will instruct the participant to visit the study site as Potential COVID-19 Illness Visits (Table 1-4). Participants diagnosed with SARS-CoV-2 infection based on the RT-PCR test result will be monitored by the study investigator or subinvestigator for 28 days. If necessary, the investigator or subinvestigator instruct a participant to visit the study site (COVID-19 Illness Visit) and undergo appropriate examinations. The participant will visit the study site 28 days after Potential COVID-19 Illness Visit for follow-up (COVID-19 Follow-up Visit). For participants who are diagnosed with COVID-19 before receiving the final vaccination, the subsequent vaccination will be cancelled, although they will continue to be assessed for the safety. While the diagnosis of COVID-19 will not be reported as an adverse event (AE), they will be reported as a serious adverse event (SAE) if they fulfill the definition of SAE.

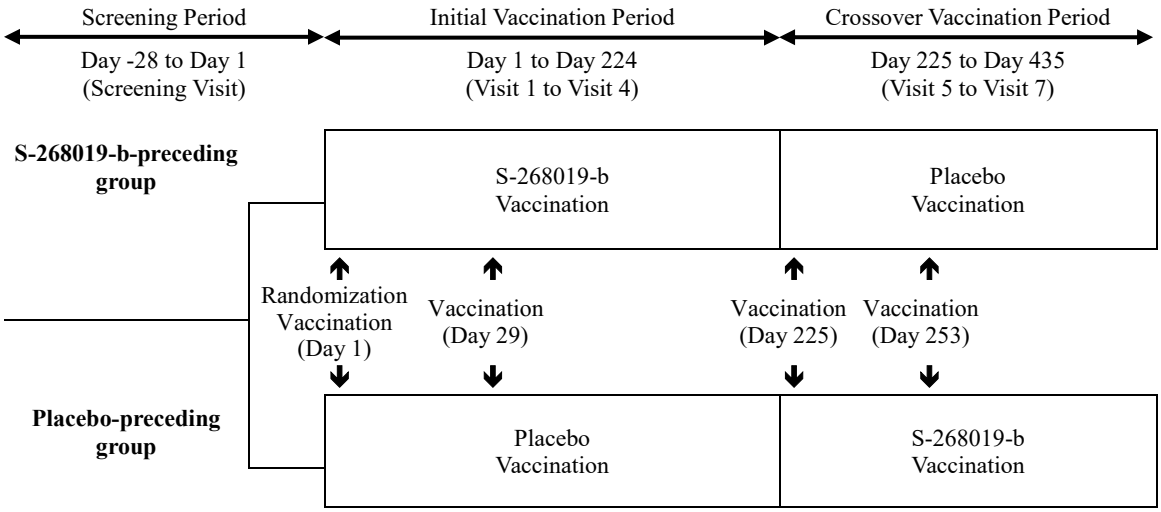
Table 1-2 Disposition of Vaccination Participants

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	

Independent Data Monitoring Committee: Yes

1.2 Schema

Figure 1-1 Study Schematic



If a participant has any of COVID-19-related symptoms (Table 8-1) during the study, he/she will visit the study site for the Potential COVID-19 Illness Visit.

1.3 Schedule of Activities (SoA)

Table 1-3 Schedule of Activities for Participants without COVID-19

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 symptoms[k]		←X→							X
	Solicited AE (reported by participants)[l]		←X[l]→							
AE review[m]		X	←X→				←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]
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 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 (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.

Table 1-4 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.

2. INTRODUCTION

S-268019-b is a recombinant protein subunit vaccine being developed by Shionogi & Co., Ltd. for prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2. S-268019-b consists of S-910823, a recombinant protein modified from SARS-CoV-2 spike glycoprotein (S-protein) as an antigen and A-910823, squalene-in-water emulsion as an adjuvant.

2.1 Study Rationale

This study will assess the efficacy, safety and immunogenicity of S-268019-b, a candidate prophylactic vaccine for the prevention of COVID-19. This study was planned to use the dose at which immunogenicity and safety were confirmed in the ongoing Phase 1/2 double-blind study of S-268019-b (2026U0221).

2.2 Background

COVID-19 was first identified in Wuhan, China, in December 2019, and has spread rapidly and globally. World Health Organization (WHO) expressed that COVID-19 could be characterized as a pandemic on March 11, 2020. Although most people infected by SARS-CoV-2 are asymptomatic or have mild symptoms, COVID-19 can also cause severe illness and even death. Some populations, including older adults and people who have certain underlying medical conditions, are at increased risk of severe illness. Globally, at the time of writing (July 2022), there have been more than 548 million confirmed cases of COVID-19, including 6 million deaths, reported to WHO [1].

SARS-CoV-2 is an enveloped β-coronavirus with a positive-sense, single-stranded RNA genome. The viral envelope is coated by S-protein, envelope, and membrane proteins [2]. The first step in infection is the virus binding to a host cell through its target receptor angiotensin-converting enzyme 2 (ACE 2). The S1 subunit of the S-protein contains the receptor binding domain that binds to the peptidase domain of ACE 2. The S2 subunit of the S-protein mediates fusion of the viral and host cell membranes, then the viral genome is delivered into the host cell [3]. The S2 subunit is highly preserved and is considered a target of vaccines against SARS-CoV-2.

Vaccines are critical tools to settle down COVID-19 pandemic. Many COVID-19 vaccines based on different technology platforms have been developed including inactivated vaccines, protein subunit vaccines, nucleic acid vaccines and viral vector vaccines. To date, five COVID-19 vaccines have been approved in the United States (US) or European Union (EU); tozinameran (Pfizer/BioNTech), mRNA-1273 (Moderna), Vaxzevria (AstraZeneca), Ad26.COV2.S (Johnson & Johnson) and Nuvaxovid (Novavax). The first two are messenger ribonucleic acid (mRNA) vaccines, the next two are adenovirus vector vaccines, and the last one is a recombinant protein vaccine. These vaccines have been shown vaccine efficacy compared to placebo in clinical studies.

As COVID-19 vaccines rollout, risks of individual vaccines have become clear. Myocarditis or pericarditis have been reported after vaccination with mRNA vaccines especially in young males [4]. For adenovirus vaccines, vaccine-induced immune

thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome (TTS) have been reported especially in young female [5]. Incidences of these significant adverse reactions are very rare, and health authorities conclude that the benefits of COVID-19 vaccines outweigh the potential risks. That being said, these potential risks are a barrier to expanded immunization of COVID-19 vaccines to younger people.

Thus, there is an urgent need to speed up the development of additional safe and effective vaccines against COVID-19 and provide them to all countries so that the world is effectively protected against COVID-19.

S-268019-b is an investigational vaccine for the prevention of the COVID-19. S-268019-b consists of S-910823, a modified recombinant S-protein produced in insect cells using the baculovirus expression vector system (BEVS) [6] as an antigen, and A-910823 (including squalene, tocopherol and polysorbate 80 as main components) as an adjuvant. A detailed description of the physical, chemical and pharmaceutical properties of S-268019-b is provided in the Investigator's Brochure [7].

As of July 8, 2022, in addition to this study, three clinical studies of S-268019-b as a priming vaccine are ongoing. In a phase 1/2 study (2026U0221), the safety, tolerability and immunogenicity of S-268019-b in Japanese adult participants are assessed. It was confirmed that there were no significant concerns with the safety and tolerability of S-268019-b 5 µg and 10 µg up to Day 50 (28 days after the second vaccination). In the phase 1/2 study, the anti-spike protein IgG antibody titer and the neutralizing antibody titer were found to be produced up to Day 50 and 10 µg was selected as the dose in further studies. In a phase 2/3 study (2114U0222) and a phase 3 study (2025U0231), the immunogenicity, safety, and clinical efficacy of S-268019-b are to be assessed. In addition, a phase 2/3 study in participants aged 12 to 19 years (2148U0225) has been initiated. Furthermore, a phase 2/3 study (2124U0223) and a phase 3 study (2140U0224) to evaluate the immunogenicity of S-268019-b as a booster vaccine is ongoing.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of S-268019-b can be found in the Investigator's Brochure [7].

3. OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are shown in Table 3-1.

Table 3-1 Study Objectives, Estimands and Endpoints

Objectives	Estimands/Endpoints
Primary	
● 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.	**Population:** Modified Intent to Treat (mITT) Population
	Endpoint: The first occurrence of SARS-CoV-2 reverse transcription polymerase chain reaction (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.
	Intercurrent events: For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint, the absence of data following these participants' withdrawal will be treated as missing; participants who withdrew before 14 days post second vaccination or who were diagnosed with SARS-CoV-2 infection prior to 14 days post second vaccination in the Initial Vaccination Period will be excluded from the primary endpoint analysis.
	Summary measure: Vaccine efficacy (VE), calculated as 1-relative risk. (Relative risk is the incidence of infection in the intervention group relative to the incidence of infection in the control group.)
Key Secondary	
● To assess the efficacy of S-268019-b for the prevention of symptomatic infection of COVID-19 as compared to placebo.	● 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.

Secondary	
● To assess the efficacy of S-268019-b for the prevention of symptomatic infection of COVID-19 as compared to placebo.	● 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.
● 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.	● 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.
● To assess the safety and reactogenicity of S-268019-b.	● The incidence of AEs, treatment-related AEs, SAEs, AESIs, MAAEs, solicited local AEs, and solicited systemic AEs, and vital signs in the Initial Vaccination Period and the Crossover Vaccination Period.
● To assess the immunogenicity of a 2-dose regimen of S-268019-b in the subset of immunogenicity subset.	● The following items for SARS-CoV-2 neutralizing antibody titer and anti-SARS-CoV-2 S-protein immunoglobulin G (IgG) antibody titers from Immunogenicity subset: – Geometric mean titer (GMT) – Geometric mean of fold rise of antibody titer (GMFR) – Seroconversion rate
Exploratory	
● To assess the durability of VE 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 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.

• To explore SARS-CoV-2 genetic variants in participants diagnosed with COVID-19.	• Nucleotide sequences of SARS-CoV-2 viral genomes detected in nasopharyngeal swabs from RT-PCR-positive participants analyzed with next-generation sequencing.

4. STUDY DESIGN

4.1 Overall Design

This 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. Participants, investigators, and other site staff except persons in charge of management, dispensing and administration of the study interventions will be blinded.

This study will consist of the Screening Period (Day −28 to Day 1), the Initial Vaccination Period (Day 1 to Day 224), and the Crossover Vaccination Period (Day 225 to Day 435). A schematic overview of the study is presented in Figure 1-1.

In the screening period, potential participants who signed the informed consent form (ICF) will be screened for study participation. On Day 1 in the Initial Vaccination Period, eligible participants will be randomly assigned to either the S-268019-b-preceding group or the placebo-preceding group in a 2:1 ratio. A total of approximately 54,915 participants will be randomized (36,610 participants in the S-268019-b-preceding group, 18,305 participants in the placebo-preceding group). The randomization will be stratified by age group (18 to 64 years of age and ≥ 65 years of age). The group allocation and vaccination schedule are shown in Table 4-1. Participants assigned to the S-268019-b-preceding group will receive S-268019-b on Day 1 and Day 29, and participants assigned to the placebo-preceding group will receive placebo on the same schedule. The Initial Vaccination Period will go on for 6 months after the second vaccination.

Table 4-1 Group Allocation and Vaccination Schedule

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	

Participants who completed the Initial Vaccination Period without being infected with SARS-CoV-2 will proceed to the Crossover Vaccination Period starting on Day 225. In the Crossover Vaccination Period, participants assigned to the S-268019-b-preceding group will receive placebo on Day 225 and Day 253 and participants assigned to the placebo-preceding group will receive S-268019-b on the same schedule. The Crossover Vaccination Period will go on after the fourth vaccination to monitor for COVID-19-related symptoms and to monitor for safety.

Participants will be assessed for the efficacy, safety, and immunogenicity in accordance with the planned schedule of activities (SoA, Table 1-3). Surveillance for COVID-19-related symptoms during the study will be performed using e-Diary. Participants will be asked to record occurrence of COVID-19-related symptoms in e-Diary once a week. The investigator or designee will receive an alert e-mail from the e-Diary system when a participant reports any COVID-19-related symptom or a participant reports symptoms that meet the criteria for COVID-19. Then the investigator or designee instructs the participant to visit the site as soon as possible but no later than 3 days from that day to collect a nasopharyngeal swab sample for reverse transcription polymerase chain reaction (RT-PCR) test. The participants will undergo the procedures described in the SoA (Table 1-4). The investigator should monitor a participant on a daily basis with information from e-Diary until RT-PCR result is available. The investigator should schedule additional site visit(s) or telehealth visit(s) depending on each participant's condition and perform additional examination as appropriate. After RT-PCR result is available, the participant with a negative RT-PCR result will return to his/her respective study schedule. On the other hand, the RT-PCR-positive participants will be further monitored until they recover from COVID-19. The COVID-19 Follow-up Visit is scheduled 28 days after the Potential COVID-19 Illness Visit. If any COVID-19-related symptom persists 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. For participants who are diagnosed with COVID-19 before receiving the final vaccination, the subsequent vaccination will be cancelled, although they will continue to be assessed for the safety.

Participants may undergo any diagnostics test for SARS-CoV-2 outside the study. Participants will be instructed to contact the site immediately when he/she obtains a result indicative of SARS-CoV-2 infection from such a test done outside the study. The investigator should assess if such results are suggestive of COVID-19 and arrange the confirmatory RT-PCR test as described above.

4.2 Scientific Rationale for Study Design

This study is designed to evaluate primarily the clinical efficacy and safety of S-268019-b in the prevention of COVID-19. Well-designed clinical studies are necessary to determine the benefit and risk of a new vaccine. A randomized, observer-blind, and placebo-controlled study is a standard for phase 3 studies of investigational vaccines.

In addition to the short-term safety and efficacy data, it is important to continue to follow up participants to provide the long-term safety and efficacy information of an investigational vaccine. On the other hand, there is argument from ethical viewpoint against including a placebo arm in a long-term blinded study. In order to address this issue, a blinded crossover design is adopted in this study. All participants assigned to placebo in the Initial Vaccination Period will receive the investigational vaccine in the Crossover Vaccination Period. All participants assigned to the investigational vaccine in the Initial Vaccination Period will receive placebo in the Crossover Vaccination Period. This crossover design ensures that all participants receive the investigational vaccine without unblinding the treatment assignment. Furthermore, the blinded crossover design enables estimation of durability of vaccine efficacy by assuming that the benefit of

vaccination over time has the same profile for the original vaccine recipients and the placebo crossovers [8].

The primary efficacy endpoint in this study is 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 seronegative and PCR-negative at baseline. Laboratory-confirmed COVID-19 is an acceptable primary endpoint for a COVID-19 vaccine phase 3 studies [9]. The vaccine efficacy will be estimated based on the primary endpoint.

4.3 Justification for Dose

The dose of S-268019-b in this study was selected based on the results from the preceding double-blind phase 1/2 study of S-268019-b (2026U0221). In the preceding phase 1/2 study, an increase in SARS-CoV-2 neutralizing antibody (NAb) titers that could be expected to prevent the onset of COVID-19 was observed at the dose selected for this study, and there were no safety or tolerability concerns.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be ≥ 18 years of age, at the time of signing the informed consent form.

Sex

2. Male and female
   a. Male

      There is no contraceptive obligation.

   b. Female:

      - A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
        – Is not a WOCBP.

        OR

        – All of the following apply:
          - Is a WOCBP and using an acceptable contraceptive method described in Section 10.3, from the first dose of study intervention through at least 90 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention.
          - A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) during the screening period before the first dose of study intervention (see Section 10.3).
          - If a urine pregnancy test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test to rule out positivity is required.
      - Additional requirements for pregnancy testing during and after study intervention are noted in Section 10.3.
      - The investigator or subinvestigator reviews medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. The investigator or subinvestigator excludes any woman considered potentially pregnant.

Informed Consent

3. Capable of giving signed informed consent form as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other Inclusion

4. Agree not to participate in any other SARS-CoV-2 prevention trial during the study follow-up.
5. Capable of using Diary without difficulties (if applicable, with assistance by caregiver).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Current or history of a laboratory-confirmed diagnosis of SARS-CoV-2 infection or COVID-19.
2. Unstable current 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.
3. Immunosuppression (immunodeficiency, acquired immunodeficiency syndrome [AIDS], use of systemic steroids, use of immunosuppressants within the past 6 months prior to the first dose of study intervention, treatment for malignant tumors, other immunosuppressive therapy).
4. 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, contraindicates participation in the study (except for pollinosis and atopic dermatitis).
5. Participant has a contraindication to intramuscular (IM) injections or blood draws.

Prior/Concomitant Therapy

6. Previous vaccination against SARS-CoV-2.
7. Any inactivated vaccine received within 14 days prior to the first dose of study intervention.
8. Any live vaccine received within 28 days prior to the first dose of study intervention.
9. Immunoglobulin preparations, blood products, or a blood transfusion within 3 months prior to the first dose of study intervention.

Prior/Concurrent Clinical Study Experience

10. Current enrollment or past participation within the last 30 days before signing of the ICF for this study in any other clinical study involving an investigational study intervention or any other type of medical research.
11. Exposure to 4 or more new chemical entities within 12 months prior to the first dose of study intervention.

Other Exclusions

12. Ineligibility for the study as considered by the investigator or subinvestigator.
13. An immediate family member or household member of this study's personnel (both the sponsor and site personnel).

5.3 Lifestyle Considerations

1. Participants must follow the contraception requirements outlined in Section 10.3.
2. Refer to Section 6.5 for prohibited and restricted prior and concomitant therapy.
3. Participants must keep their e-Diary as per instructions.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to, or used by, a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

Outlines of the study interventions are summarized in Table 6-1. Since S-268019-b and placebo are distinguishable by appearance, a pharmacist to prepare study vaccines and a vaccine administrator will be unblinded. The unblinded pharmacist and vaccine administrator must not communicate with participants, investigators, or other site staff about participant's treatment assignment.

Table 6-1 Study Intervention(s)

	Test Vaccine		Placebo
Study Intervention Name	S-268019 solution for intramuscular injection (containing S-910823) 40 µg/mL	S-268019 oil-in-water emulsion adjuvant	Placebo (physiological saline)
Dosage formulation	Solution for IM injection	Emulsion for IM injection	Solution for IM injection
Container	Vial	Vial	Prepared locally by a qualified site personnel
Filling volume	Each vial contains 2 doses of 0.25 mL.	Each vial contains 2 doses of 0.25 mL.	Prepared locally by a qualified site personnel
Dosage level(s)	One dose contains 10 µg of S-910823 (antigen) in 0.25 mL	Each vial contains 1 mL of A-910823 (for the Initial Vaccination Period) Each vial contains 0.9 mL of A-910823 (for the Crossover Vaccination Period)	Placebo
Dosage and Administration	S-268019 solution for IM injection (containing S-910823) 40 µg/mL and S-268019 oil-in-water emulsion adjuvant are mixed at a ratio of 1:1 (each 0.25 mL for one dose), and 0.5 mL of the mixture is administered at a 4-week interval for a total of two doses.		A dose of 0.5 mL is administered at a 4-week interval for a total of two doses.
Route of Administration	IM injection		
Use	Investigational vaccine (antigen)	Investigational vaccine (adjuvant)	Placebo as comparator
IMP and NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor		Prepared locally by a qualified site personnel
Packaging and Labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.		Not applicable

IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product

The vaccination should be given in the upper arm and, if a solicited local adverse event (see Section 8.4.6) occurs after the vaccination, the next vaccination of study intervention may be given in an arm different from that receiving the previous vaccination.

S-268019-b

The investigational vaccine used in this study is composed of S-268019 solution for IM injection (containing S-910823) 40 µg/mL as an antigen and S-268019 oil-in-water emulsion adjuvant (A-910823). S-910823 is a recombinant protein modified from

S-protein of SARS-CoV-2. A-910823 is squalene-in-water emulsion. S-910823 and A-910823 are supplied in different vials. The vaccine (ie, S-268019-b) is a 1:1 mixture of antigen and adjuvant. Please refer to the study vaccine manual for instructions on how to prepare the study vaccine.

Placebo

Commercially available 0.9% (w/v) physiological saline for injection will be used for placebo. Placebo will be sourced locally.

6.2 Preparation/Handling/Storage/Accountability of Study Intervention

1. Before unblinding the assignment of participants to the intervention groups at the time of the primary immunogenicity analysis, the unblinded pharmacist or designee will maintain accurate records of the following information; receipt and condition of all study drugs, date of the receipt, when and how much the study intervention was dispensed and administered to each participant in the study, date and time of reconstitution, and any reasons for departure from the protocol-defined regimen. The unblinded pharmacist or designee must confirm that appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The drug accountability records and the used vials should be available for verification by the unblinded sponsor monitor, unblinded contract research organization (CRO), or designee at each monitoring visit as specified in the unblinded clinical operations plan. If the local procedures at a site require immediate disposal of used vials, an alternative process for drug accountability will be made with the site and the process will be documented in the study files.
4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manuals.

6.2.1 Dose Preparation and Dispensing

All study interventions must be stored in a secured location with limited access and at controlled temperatures as indicated on the product labels. If a study intervention is exposed to temperatures outside the specified temperature range, all relevant data will be sent to the sponsor to determine if the affected supplies can be used or will be replaced.

The affected study intervention must be quarantined and not used until further instruction from the sponsor is received.

Doses of S-268019-b and placebo will be prepared by an unblinded pharmacist at the study site, who will not be involved in any other study procedures. The unblinded pharmacist will obtain the treatment assignment information from an Interactive Web Response System (IWRS) at Days 1, 29, 225 and 253, and draw S-268019-b or placebo into a syringe labeled with the participant's identification number. The unblinded pharmacist will provide the syringe to an unblinded vaccine administrator. The unblinded pharmacist and administrator must not communicate with the investigator or other site staff about the participant treatment assignment.

6.2.2 Administration

Participants will visit the study sites and receive one dose of study intervention at each vaccination visit (Days 1 and 29 in the Initial Vaccination Period and Days 225 and 253 in the Crossover Vaccination Period). The investigator or designee should confirm participant's eligibility for vaccination prior to each vaccination (see Section 6.2.3).

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an unblinded administrator. Participants will remain under observation by blinded site staffs for at least 30 minutes after each vaccination to monitor for the development of acute allergic reactions.

6.2.3 Criteria for Delay of Study Vaccination

The investigator or subinvestigator should confirm that participants meet the following two conditions at the time of each vaccination. If either of the following conditions is not met, the vaccination on that day will be postponed. Out of window vaccination is allowed for this reason.

1. Participants with axillary temperature < 37.5°C or oral temperature < 38.0°C
2. Participants considered by the investigator or subinvestigator to have no problems with vaccination

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

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 SoA (Table 1-3). 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.

6.3.2 Blinding

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 S-268019-b and placebo. 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. Procedures for maintaining blinding will be specified separately.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. The investigator should get the participant's intervention assignment information from IWRS, but not from the site unblinded pharmacist or qualified designee. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and IWRS, as applicable.

If investigators receive requests to unblind study participants who become eligible to receive an authorized/licensed COVID-19 vaccine, the investigator will discuss with the participant available options and ramifications. If the participant is eligible for an authorized/licensed vaccine according to local immunization guidelines or recommendation and if the participant wishes to proceed with the unblinding, the investigator will follow the unblinding procedures. The reason for the unblinding request should be documented. The name and dates of administration of the other COVID-19 vaccine should be recorded. When unblinding, if it is determined that the participant received S-268019-b, the participant will be informed that there are not sufficient data on the safety of receiving other COVID-19 vaccines in addition to S-268019-b. Unblinded participants, whether in the S-268019-b-preceding group or placebo-preceding group, will be asked to continue to be followed in this study in line with the schedule of activities to the extent that they permit. Efficacy and safety evaluations will be identical for all participants, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study, including participants in the safety subset, if applicable and feasible. All data will be analyzed

separately from the point of unblinding, for safety and efficacy analysis, as described in the Statistical Analysis Plan.

6.4 Study Intervention Compliance

The unblinded vaccine administrator will administer the study intervention to participants at the study sites. The date and time of each vaccination will be recorded in the source documents and the date will be recorded in the electronic case report form (eCRF). Study participant identification will be confirmed at the time of dosing by the study site staff other than the vaccine administrator.

The investigator or site staff should have participants visit the study site within the specified visit windows. If a participant doesn't come to the study site on an appointed day, every effort should be made to contact the participant and complete a visit within the specified visit window. The vaccination will not be cancelled even if a participant comes to the study site outside the time window.

6.5 Prior Therapy/Concomitant Therapy

Prior therapies (prior medications/therapies) are those taken prior to the first dose of study intervention (prescription medications, over-the-counter medications/herbal medicines, and non-drug therapies). Restrictions regarding prior therapies are specified in the exclusion criteria.

Concomitant therapies (concomitant medications/therapies) are those taken after the first dose of study intervention until the time of the end-of-study/early discontinuation examination (prescription medications, over-the-counter medications/herbal medicines, and non-drug therapies).

Prohibited Concomitant Medications/Therapies

The use of following medications/therapies will be prohibited from the time of informed consent to Day 435 or completion of the tests at discontinuation.

- SARS-CoV-2 vaccine
- Corticosteroids (oral, injection, suppository, or enema only)
- Immunosuppressants (oral, injection, suppository, or enema only)
- Any other investigational study intervention

Even if a participant takes a prohibited medication, the participant will continue the study and undergo the scheduled examinations.

When the latest information on the S-268019-b is obtained, the investigator or designee will provide the information to participants and recommend an authorized/approved vaccine to participants, considering safety information. If participants wish receipt of an authorized/approved vaccine depending on the information, the investigator or designee

will consider safety and make a decision whether these participants can get an authorized/approved vaccine. In that case, the participant must discontinue the study intervention. And if the participant could not get the second dose of study intervention, the participant must discontinue the study participation.

Restricted Concomitant Medications/Therapies

The use of following medications/therapies will be prohibited from the time of informed consent to completion of the tests to be performed on Day 253.

- Non-SARS-CoV-2 vaccines
- Blood-derived immunoglobulin preparations
- Blood products
- Transfusions

All prior therapies used/administered within 7 days prior to the first dose of study intervention and all concomitant therapies (prescription medications, over-the-counter medications, and non-drug therapies) used by participants at the time of study intervention during study period must be recorded except during Day 58 to 224 and Day 254 to 435, in which only concomitant medication for treatment of SAE, MAAE, or AESI, or prohibited medication will be collected. These therapies are recorded in the eCRF along with:

- Reason for use
- Dates of use including start and end dates
- Route of administration

The sponsor should be contacted if there are any questions regarding acceptable concomitant or prior therapy.

6.6 Dose Modification of Study Intervention

This protocol allows neither dose modification nor changes to the number of doses of the study intervention.

6.7 Intervention after the End of the Study

No medical/vaccination intervention for the prophylaxis of COVID-19 will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

7.1 Discontinuation or Suspension of Entire Study and Participant Discontinuation or Suspension

7.1.1 Discontinuation or Suspension of the Entire Study

The sponsor may prematurely terminate or suspend the entire study for the following reason:

- Ensuring safety of the study is difficult due to safety concerns (eg, occurrence of many serious treatment-related AEs)

7.1.2 Discontinuation or Suspension of Individual Participants

Participants will be discontinued from the study if any of the following criteria are met:

At the time of discontinuing from the study participation, an early discontinuation examination should be conducted as far as possible, as shown in the SoA. Refer to the SoA (Section 1.3) for data to be collected at early discontinuation. If possible, collection of safety data will be continued from participants who discontinue from the study participation after administration of study intervention.

Criteria for Discontinuation of Study Participation

- The participant requests to discontinue study participation
- The participant is lost to follow-up
- The participant died
- The participant meets the criteria for discontinuation of study intervention after the first vaccination and could not receive the second dose of study intervention
- The investigator or subinvestigator considers that the participant should be withdrawn from study participation for any other reasons

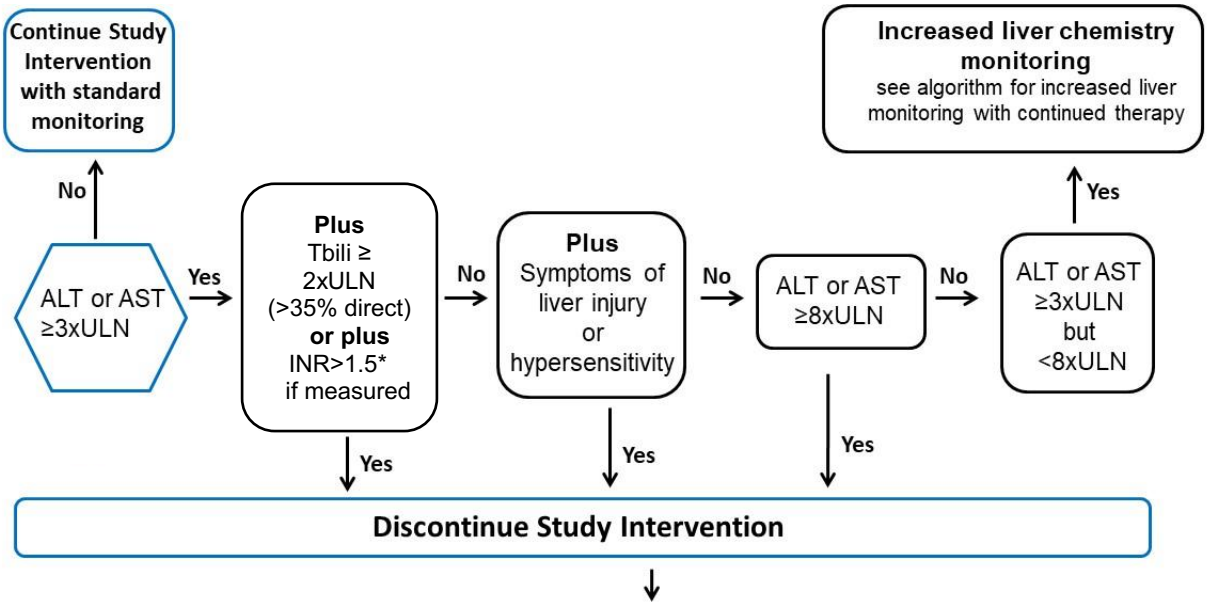
Criteria for Discontinuation of Study Intervention after the First Vaccination

- The participant is found to be infected with SARS-CoV-2 based on the RT-PCR test at the Potential COVID-19 Illness Visit. However, if the participants who are infected with SARS-CoV-2 after second dose wish to receive the study intervention in the Crossover Vaccination Period and the investigator or subinvestigator considers that they have no problems with vaccination on Day 225 and Day 253, they will be able to receive the study intervention and continue the study schedule.
- The participant received any approved SARS-CoV-2 vaccine
- The participant became pregnant
- A serious or intolerable AE occurs after the first dose of study intervention and the investigator or subinvestigator considers that the further study intervention should be discontinued

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 8 × Upper limit of normal (ULN)
- ALT or AST ≥ 5 × ULN but < 8 × ULN persists for ≥ 2 weeks, or ALT or AST ≥ 3 × ULN but < 5 × ULN persists 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 measured
- ALT or AST ≥ 5 × ULN but < 8 × ULN and cannot be monitored weekly for ≥ 2 weeks, or ALT or AST ≥ 3 × ULN but < 5 × ULN and cannot be monitored weekly for ≥ 4 weeks
- ALT or AST ≥ 3 × ULN with appearance or worsening of symptoms believed to be related to liver injury or hypersensitivity

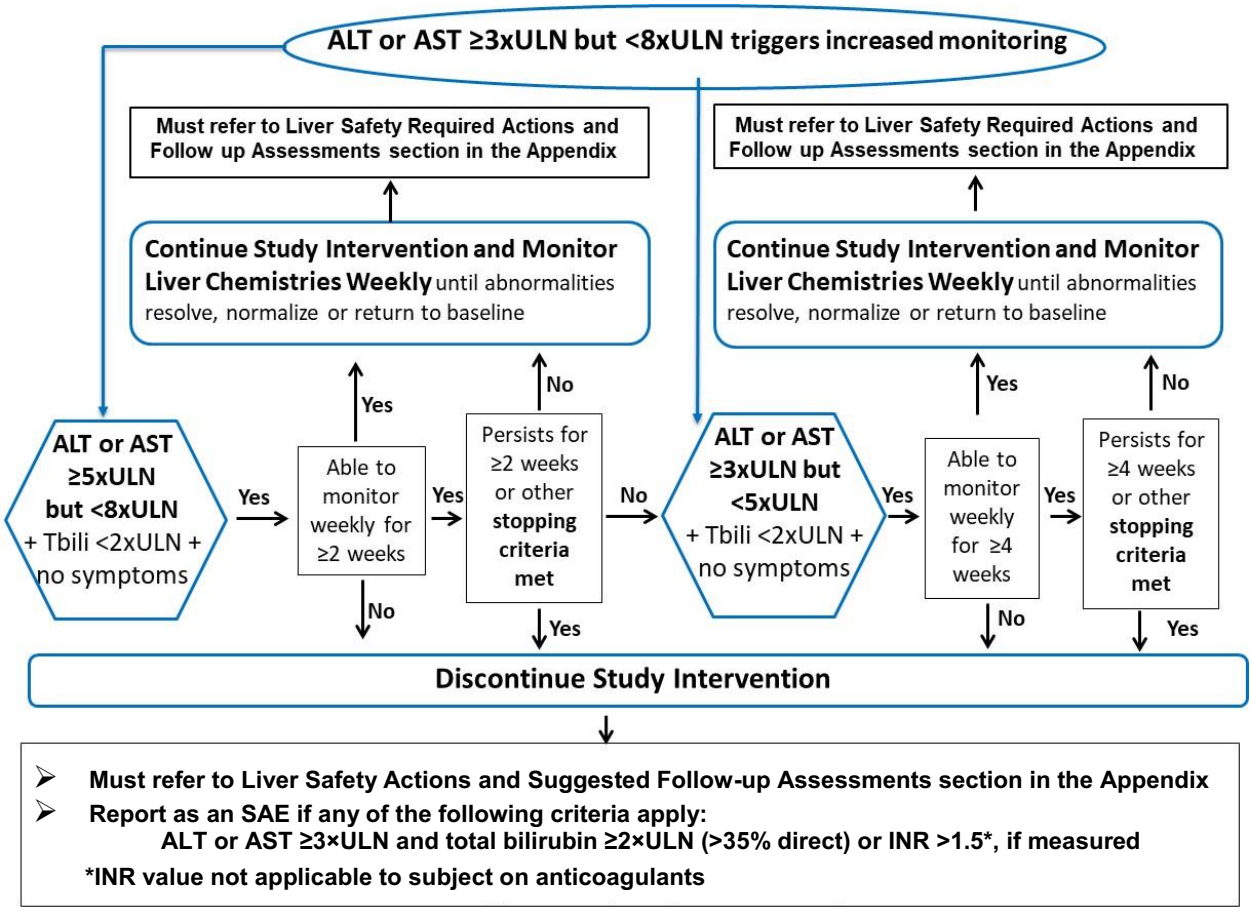
Study intervention will be discontinued **for a participant** if liver chemistry stopping criteria are met.

Figure 7-1 Phase 3-4 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase, INR = international normalized ratio; SAE = serious adverse event, Tbili = Total bilirubin; ULN = upper limit of normal

Figure 7-2 Phase 3-4 Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT or AST ≥ 3 × ULN but < 8 × ULN



Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase, INR = international normalized ratio; SAE = serious adverse event, Tbili = Total bilirubin; ULN = upper limit of normal

Liver Safety: Suggested Actions and Follow-up Assessments can be found in Section 10.5.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. However, unless there is a safety reason, the participant should only be withdrawn from study drug administration, while continuing to remain in the trial and continuing to follow the SoA scheduled visits, even while off-vaccine to protect the integrity of the study and the participant's well-being.
- If the participant withdraws consent, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Table 1-3). See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site staff must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant by phone and the contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1-3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator must maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The investigator should investigate the following information according to the SoA (Section 1.3). The investigator or designee should record the result of investigation in the eCRF.

- Demographics
  Year of birth, age at the time of signing the informed consent form, sex, ethnicity, race, smoking status, medical history (all complications persist at the time of signing the informed consent form, significant medical history requiring hospitalization or surgery within 12 months prior to signing the informed consent form)
- Body measurement
  Height, body weight, body mass index (BMI) (automatically calculated by electronic data capture system [EDC])

8.1 Assessment Tool

8.1.1 Electronic Clinical Outcome Assessment (e-Diary)

An electronic clinical outcome assessment (e-Diary) tool will be used in this study. The e-Diary uses either an application downloaded to participant's smartphone/tablet or a device that is provided to participants at the time of enrollment. The e-Diary tool will be provided in the local language.

The e-Diary will be used for the following purposes.

- To surveil COVID-19-related symptoms.

- To collect solicited local and systemic AEs during 7 days after the first and second vaccinations (e-Diary)

On Day 1 and at the Potential COVID-19 Illness Visit, participants (or their caregiver, if applicable) will be trained on how to use the e-Diary tool. A user manual will be provided to participants. A Help Desk will be available for technical support. Participants who confirmed not to be able to use the e-Diary should use paper diaries. Those participants will be trained on how to use the paper diaries.

8.2 Efficacy Assessments

In this study, the vaccine breakthrough cases will be investigated as an efficacy assessment.

8.2.1 Definition of Symptomatic COVID-19

A patient is defined to have symptomatic COVID-19 when the patient's RT-PCR test result is positive and he or she has at least one of the following COVID-19-related symptoms (Table 8-1). The medical monitor of the sponsor will confirm whether each potentially symptomatic patient has symptomatic COVID-19 or not.

Table 8-1 COVID-19-related Symptoms

Duration	Symptom
No minimum duration	Fever (Oral ≥ 38.0°C [≥ 100.4°F] or Axillary ≥ 37.5°C [≥ 99.5°F])
	Shortness of breath
	Difficulty breathing
Must be present for ≥ 2 days	Chills
	Cough
	Fatigue
	Muscle aches
	Body aches
	Headache
	New loss of taste
	New loss of smell
	Sore throat
	Congestion
	Runny nose
	Nausea

Duration	Symptom
	Vomiting
	Diarrhea

Modified from Centers for Disease Control and Prevention (CDC) 2020 [10].

8.2.2 Severity of COVID-19

If a participant is confirmed to have symptomatic COVID-19, the investigator will evaluate if the maximum intensity during the course of the disease meets the criteria for severe 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, pulse rate ≥ 125 beats per minute, oxygen saturation ≤ 93% on room air at sea level, or partial pressure of oxygen to fraction of inspired oxygen ratio < 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

The investigator will record the severity (severe or not), start and end dates, and the presence or absence of RT-PCR tests result outside the study sites (if performed) in the eCRF. The date of onset of COVID-19 is defined as the date when a symptom associated with COVID-19 is first reported.

A hospitalization due to COVID-19 must be reported as an SAE (Section 10.2.4). Details of treatments/procedures in response to the SAE such as oxygenation, ventilation, transfer to an ICU should be described.

8.2.3 Surveillance for COVID-19-related Symptoms

Surveillance of COVID-19-related symptoms will be performed throughout the study (after the first vaccination and until the end of the study) using an e-Diary tool. The e-Diary uses either an application downloaded to participant's smartphone/tablet or a device that is provided to participants at the time of enrollment. The e-Diary tool will be provided in the local language.

On Day 1 and at the Potential COVID-19 Illness Visit, participants (or their caregiver, if applicable) will be trained on how to use the e-Diary tool. A user manual will be provided to participants. A Help Desk will be available for technical support. The questionnaire on

the e-Diary asks if a participant had any of COVID-19-related symptoms. Participants will complete the questionnaire for COVID-19-related symptoms at least once a week or whenever they experience any new or worsened COVID-19-related symptoms.

The investigator or designee will receive an alert e-mail from the e-Diary system when a participant reports any COVID-19-related symptom. The investigator or designee will review the information in the e-Diary. If any COVID-19-related symptom (Table 8-1) is suspected, the investigator or designee will instruct the participant to visit the site for the Potential COVID-19 Illness Visit (Section 8.2.5.1) as soon as possible but within 3 days after the investigator or designee realizes the symptom. The investigator or designee records the date of instruction in the eCRF if they instruct participants to visit, and records the reason in the source record if they did not instruct a visit. If the e-Diary cannot be used for some reason, the investigator or site staff will instruct the participants to record the presence or absence of COVID-19-related symptoms on a paper diary, and instruct the participants at every visit to contact the study site promptly if they experience any new COVID-19-related symptoms.

In addition, if the participant's condition suddenly changes, the investigator or subinvestigator should instruct the participant in advance so that the participant or the participant's family will notify the study site by telephone or the like. When notified by the participant or the participant's family, the investigator or subinvestigator will collect information about the participant's COVID-19-related symptoms.

It should be noted that some of COVID-19-related symptoms overlap with solicited systemic AEs (ie, fever, chills, nausea/vomiting, diarrhea, headache, fatigue, myalgia). In principal, these events that occur during the 7 days following each vaccination should not trigger a Potential COVID-19 Illness Visit unless, in the investigator’s opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity.

8.2.4 SARS-CoV-2 RT-PCR Test

Nasopharyngeal swab samples will be collected before the first vaccination on Day 1 to determine a modified intent-to-treat (mITT) population and on Potential COVID-19 Illness Visit for judgement of symptomatic COVID-19. The samples will be sent to central laboratories for the SARS-CoV-2 RT-PCR test. Instructions for obtaining mid-turbinate nasopharyngeal swabs samples and shipping to the central laboratory are provided in the Laboratory Manual. The result will be reported to the study site after sample arrival at the central laboratory. The SARS-CoV-2 RT-PCR test on Day 1 and additional (qualitative or quantitative) PCR test may be performed at study sites or local laboratories in accordance with local regulations or institutional standards; however, the final diagnosis of SARS-CoV-2 infection after the vaccination must be based on the results from the central laboratory.

8.2.5 Procedures in the Event of Suspected COVID-19

8.2.5.1 Potential COVID-19 Illness Visit

At the Potential COVID-19 Illness Visit, a participant will undergo the procedures described in the SoA (Table 1-4). 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. The RT-PCR test must be performed to confirm SARS-CoV-2 infection. The investigator or site staff will contact the participant once a result of the RT-PCR test is available. The participant with a negative RT-PCR result will return to his/her respective study schedule. On the other hand, the RT-PCR-positive participants will be further monitored until they recover from COVID-19. Participants will self-evaluate COVID-19-related symptoms and record in the e-Diary daily until all symptoms have disappeared. The investigator should carefully monitor a participant and give a participant adequate treatment in accordance with applicable local/international treatment guideline and/or institutional standard until the participant has fully recovered or been medically stable.

8.2.5.2 COVID-19 Illness Visit

For a participant confirmed to have symptomatic COVID-19, the investigator should schedule additional site visit(s) or telehealth visit(s) depending on participant's condition and perform additional examination as appropriate (this is referred to as "COVID-19 Illness Visit"). Such additional examinations include physical examination, vital signs, peripheral capillary oxygen saturation (SpO_2), blood gas analysis, chest X-ray or computed tomography (CT). If such additional tests are performed, the investigator will record the test results in the eCRF.

8.2.5.3 COVID-19 Follow-up Visit

The participant confirmed to have COVID-19 will be monitored until he/she clinically recovers (and, if requested by local regulations, has negative RT-PCR results on two sequential samples taken at least 24 hours apart). The COVID-19 Follow-up Visit is scheduled 28 days after the Potential COVID-19 Illness Visit to confirm if the participant has fully recovered or has been medically stable. If any COVID-19-related symptom persists 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.

8.2.6 Definition of Asymptomatic COVID-19

Asymptomatic SARS-CoV-2 infection is defined as a case in which a participant has positive result of anti-SARS-CoV-2 N-protein antibody test and does not meet the criteria of symptomatic COVID-19 (Section 8.2.1). For asymptomatic SARS-CoV-2 positive participants, Potential COVID-19 Illness Visit is not performed unless the participant reports COVID-19 symptoms.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1-3).

For any abnormal findings of safety assessments (eg, physical examination, vital signs) that worsen following exposure to the study drug from baseline, the investigator will consider whether those results are clinically significant. Any test results which are considered to be clinically significant by the investigator are to be recorded as adverse events (AEs). If abnormal laboratory finding is associated with disease or organ toxicity, the investigator should report only the disease or organ toxicity as an AE.

The investigator will consider test results to be clinically significant in the following circumstances (at their own discretion in the other circumstances):

- Test results that lead to any of the outcomes included in the definition of a serious adverse event (SAE) (See Section 8.4).
- Test results that lead to a dose interruption or discontinuation from the study.
- Test results that lead to a concomitant drug treatment or other therapy.
- Test results that require additional diagnostic testing (except for a confirmatory test) or other medical intervention.
- Test results that meet the management and stopping criteria for abnormal liver function tests identified in Section 7.1 and 10.5.

In addition, when any test results meet the management and stopping criteria for liver function abnormalities (Section 7.1 and Section 10.5) including tests conducted outside the study, the results of further assessments and required follow-up should be recorded in the Liver Event Form.

8.3.1 Physical Examinations

A complete physical examination will be performed at screening followed by brief physical examinations as specified in the SoA (Table 1-3).

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

Vital signs will be measured during the study as specified in the SoA (Table 1-3).

- Body temperature (oral or axillary), pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for immunogenicity assessments) will consist of 1 pulse rate and 1 blood pressure measurements.
- In addition to vital signs mentioned above, SpO_2 will be measured using a pulse oximeter during the COVID-19 Illness Visit (Table 1-4). It should be noted that multiple factors can affect the accuracy of a pulse oximeter reading, such as poor circulation, skin pigmentation, skin thickness, skin temperature, current tobacco use, and use of fingernail polish.

8.3.3 Pregnancy Test

A pregnancy test (urine or serum as required by local regulations) for participants of childbearing potential will be performed at screening and when it is deemed necessary by the investigator or subinvestigator in the first 57 days of each period.

Refer to Section 8.4.5 for the pregnancy reporting. Female participants who have a positive pregnancy test before the last vaccination of the study intervention should receive no further study intervention but should be followed-up for safety.

8.4 Adverse Events, Serious Adverse Events, Medically Attended Adverse Events and Adverse Events of Special Interest

AEs reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) must be captured in source documents.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE, medically attended adverse event (MAAE, see Section 8.4.7) or adverse event of special interest (AESI, see Section 8.4.8) and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7.2).

8.4.1 Time Period and Frequency for Collecting AE, SAE, MAAE and AESI Information

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). All SAEs, MAAEs and AESI will be collected from the date of signing of the ICF until end of the study.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.2.4. The investigator will report any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study (out of period specified in SoA in Section 1.3), and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.2.3.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

8.4.5 Pregnancy

- Details of all pregnancies in female participants will be collected from the first dose of study intervention through at least 90 days after the last dose of study intervention.

- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.3.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.6 Reactogenicity

The term "reactogenicity" refers to the property of a vaccine of being able to produce common solicited adverse reactions, especially excessive immunological responses and associated signs and symptoms. In order to assess the reactogenicity of S-268019-b, predefined solicited local and systemic AEs (Table 8-2) occurring after the first and second vaccinations and until 7 days post-vaccination will be collected using e-Diary.

Table 8-2 Solicited Local and Systemic Adverse Events

Solicited Local Adverse Events	Solicited Systemic Adverse Events
• Pain • Erythema/Redness • Induration • Swelling	• Fever (Oral ≥38.0°C [≥100.4°F] or Axillary ≥37.5°C [≥99.5°F]) • Nausea/Vomiting • Diarrhea • Headache • Fatigue • Myalgia

Participants will record occurrences of the solicited AEs on the day of each vaccination and for the 7 days after vaccination, preferably on the same time each day. Severity of solicited AEs will be graded in accordance with the US FDA guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Section 10.4) [11]. For erythema/redness, induration and swelling, participants will measure the longest diameter and record it in an e-Diary. For solicited systemic AEs and local pain, participants will self-evaluate the severity of the events. The investigator should review e-Diaries and enter the relevant information in the solicited AE form of the eCRF. If a solicited AE meets the criteria for SAEs or MAAEs, it should be reported as SAEs or MAAEs. If the e-Diary cannot be used for some reason, the investigator or site staff will instruct the participants to record the presence or absence of the solicited AEs and the severity of the events on paper diary.

If a solicited local or systemic AE continues beyond 7 days after dosing, an outcome of such event will be recorded in the eCRF. The investigator or site staff will contact a participant by phone to follow-up the event.

8.4.7 Medically Attended Adverse Events

An MAAE is defined as an AE leading to medically-attended visits that were not routine study visits, for example, hospital, emergency room (ER), urgent care clinic, or other visits to or from medical personnel for an AE. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled illness visits will not be considered MAAEs. An MAAE can be serious or non-serious. All MAAEs will be recorded in the eCRF. Serious MAAEs will be recorded and reported as per Section 8.4.4.

8.4.8 Adverse Events of Special Interest

Potential immune-mediated diseases will be collected as AESIs of S-268019-b [12, 13]. Details are provided in Section 10.6. AESIs can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as described in Section 8.4.4.

8.4.9 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

When a participant experiences a symptom corresponds to COVID-19-related symptoms, the investigator should carefully evaluate the relationship to COVID-19 as well as the relationship to the study intervention. Diagnosis of COVID-19 will not be recorded in the AE section of the eCRF unless it meets the criteria for an SAE.

All events that meet the definition of an SAE will be reported as an SAE according to the standard process for expedited reporting of SAEs.

8.4.10 Special Situations - Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error of the study drug (Special Situations, as defined below) must be reported to the sponsor (OR sponsor's medical monitor) via e-mail by the investigator using a Special Situations Report Form (paper form) as soon as possible. If there are associated SAEs, the investigator must also complete and submit an SAE submission in EDC or using the paper SAE form as well.

- Abuse - Persistent or sporadic, intentional excessive use of a study drug(s), which is accompanied by harmful physical or psychological effects.
- Misuse - Intentional and inappropriate use of a study drug(s) other than as directed or indicated at any dose.
- Overdose - Intentional or unintentional intake of study drug(s) in excess of the assigned dose in the protocol.
- Medication Error - Any unintended error in the prescribing, dispensing or administration of a study drug(s) (including intercepted error).

8.5 Treatment of Overdose

In this study, any dose of study intervention greater than the doses specified in the protocol and doses more than 4 in total will be considered an overdose.

sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
2. Contact the medical monitor immediately.
3. Document the quantity of the excess dose as well as the duration of the overdose in Special Situations Report Form.

Decisions regarding interruptions of vaccination will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

PK parameters are not evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8 Genetics (Virus Genome Sequencing)

Genetic variants of a virus arise as a natural by-product of viral replication. Some genetic variants of SARS-CoV-2 have been reported to date (such as 20I/501Y.V1, 20H/501Y.V2, 20J/501Y.V3). In general, variants that confer a competitive advantage with respect to viral replication, transmission, or escape from immunity will increase in frequency. Since S-protein is a major target of COVID-19 vaccines, it becomes the focus of public interest whether or not mutations in the S-protein compromise vaccine effectiveness. In this study, nasopharyngeal swab samples will be collected at the Potential COVID-19 Illness Visit (SoA, Table 1-4). Nucleotide sequences of SARS-CoV-2 strains isolated from participants diagnosed with COVID-19 will be analyzed to explore potential relationship between types of variants and efficacy of the investigational vaccine.

Virus RNA will be extracted from nasopharyngeal swab samples collected from participants at (Potential) COVID-19 Illness Visit, and nucleotide sequences will be analyzed using the next-generation sequencing technology at the central laboratory. Detailed procedures for sample collection, processing, and shipping to the central laboratory will be specified in the Laboratory Manual. The remaining samples will be disposed in accordance with guidance of the central laboratories.

8.9 Biomarkers

Biomarkers are not evaluated in this study.

8.10 Immunogenicity Assessments

Anti-SARS-CoV-2 N-protein antibodies

Blood samples will be collected from all participants at the time points shown in Table 1-3. Blood samples will be shipped to the central laboratory for the immunogenicity assessments. These samples will be analyzed for all participants.

Anti-SARS-CoV-2 S-protein IgG antibodies and SARS-CoV-2 neutralizing antibodies

Blood samples will be collected from at least 650 participants at the time points described in Table 1-3 and participants who are suspected/confirmed to have COVID-19 at the time points described in Table 1-4. Blood samples will be shipped to the central laboratory for the immunogenicity assessment.

Collection, processing, and shipment of the samples are described in the Laboratory Manual. The total blood sampling volume per participant will be approximately 36 mL.

The assays will be performed using validated assay methods (Table 8-3). The details of the analyses will be provided in a separate document.

Table 8-3 Immunogenicity Assessments

Analytes	Method
Anti-SARS-CoV-2 S-protein IgG antibodies	Chemiluminescence immunoassay [CISA]
Anti-SARS-CoV-2 N-protein antibodies	Chemiluminescence immunoassay [CLIA]
SARS-CoV-2 neutralizing antibodies	Live virus neutralization assays

Antibody titers before and after vaccination will be determined and geometric mean titer (GMT), geometric mean of fold rise of antibody titer (GMFR), and seroconversion rate will be calculated.

8.11 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary efficacy endpoint is a binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 occurring during six months from 14 days post second vaccination in the Initial Vaccination Period. Otherwise, a participant is not defined as a COVID-19 case as the primary efficacy endpoint. Vaccine Efficacy (VE) will be calculated as 1-relative risk, which is the incidence of infection in the S-268019-b-preceding group (S-268019-b) relative to the incidence of infection in the placebo-preceding group (placebo). The null hypothesis is that VE is less than or equal to 30%; whereas, the alternative hypothesis is that VE is above 30%. That is:
null hypothesis: VE ≤ 30% vs; alternative hypothesis: VE > 30%

9.2 Sample Size Determination

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.

9.3 Populations for Analyses

The following analysis populations will be defined and analyzed for this study based on enrolled participants with Good Clinical Practice (GCP) compliance.

Population	Description
Enrolled	All participants who sign the ICF.
Randomized	All participants randomly assigned to study intervention.
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.

Population	Description
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.
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.
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.
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.
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.

9.4 Statistical Analyses

The statistical analysis plan will be fixed prior to unblinding and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

In principle, quantitative variables will be summarized using the number of non-missing participants, arithmetic mean, standard deviation (SD), median, minimum, and maximum as summary statistics. Categorical variables will be summarized using frequency and percentage of participants in each category as summary statistics.

Unless otherwise noted, all statistical tests will be performed at the two-sided significance level of 0.05.

9.4.2 Disposition of Participants

The number and percentage of participants who complete the study and prematurely discontinue the study will be summarized by intervention group and by intervention period. Reason for study discontinuation will also be summarized by intervention group.

The number and percentage of participants in each analysis set will be presented by intervention group.

9.4.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by intervention group using summary statistics for the Safety Analysis Set and mITT population.

9.4.4 Intervention Compliance

Intervention compliance will be summarized by intervention group and by intervention period using summary statistics for the Safety Analysis Set.

9.4.5 Concomitant Medications and Therapies

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODD). For the Safety Analysis Set, participants who received concomitant medications or therapies will be summarized by intervention group and by intervention period.

9.4.6 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. The analysis of data generated in the Crossover Vaccination Period will be performed using the approach described by Follmann et al [15].

9.4.6.1 Primary Efficacy 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.

9.4.6.2 Key Secondary Efficacy Endpoint

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.

9.4.6.3 Secondary Efficacy and Immunogenicity Endpoint

The 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.

- The following items for SARS-CoV-2 neutralizing antibody titer and anti-SARS-CoV-2 S-protein immunoglobulin G (IgG) antibody titers from Immunogenicity subset:
  - Geometric mean titer (GMT)
  - Geometric mean of fold rise of antibody titer (GMFR)
  - Seroconversion rate

9.4.6.4 Exploratory Efficacy and Immunogenicity Endpoint

The exploratory endpoints are:

- 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 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.

- Nucleotide sequences of SARS-CoV-2 viral genomes detected in nasopharyngeal swabs from RT-PCR-positive participants analyzed with next-generation sequencing.

9.4.7 Analysis of Primary Endpoint

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

As the primary efficacy analysis, the plan is to use a Poisson regression model with robust variance to analyze the primary endpoint, which will include age as a baseline covariate as well as the log of the follow-up time as an offset [16]. The VE will be estimated from the model, which will give the relative risk 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). 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). The interim analysis will be carried out when approximately 50% (33 cases) and 75% (50 cases) of the total amount of statistical information is available. If the Poisson regression model with robust variance fails to converge, an alternative approach will be implemented.

Supplemental analysis using the same method as the primary efficacy analysis on the mITT Population will be conducted in the FAS and the PPS. In addition, 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.

9.4.8 Analysis of Secondary Endpoint(s)

The (key) secondary efficacy endpoints will be analyzed using the same manner as the primary efficacy analysis.

The secondary immunogenicity endpoints will be analyzed using the Immunogenicity Subset. For the serum levels for SARS-CoV-2 neutralizing antibody and anti-spike protein IgG antibody, the GMT at each study visit, and the GMFR comparing to the baseline at each post-vaccination study visit, along with 95% confidence interval (CI) will be summarized by intervention group. The 95% CI will be calculated based on the *t* distribution of the log-transformed values for GMT or GMFR, then back transformed to the original scale for presentation. For SARS-CoV-2 neutralizing antibody and anti-S-protein IgG antibody seroconversion at each post-vaccination study visit, seroconversion rate, along with 95% CI will be estimated for each intervention group. The 95% CI will be calculated using the Clopper-Pearson method. Seroconversion rate is defined as the percentage of participants with a ≥4-fold increase in post-vaccination antibody titer from baseline.

9.4.9 Analysis of Exploratory Endpoint(s)

The analysis for exploratory efficacy endpoints generated in the Crossover Vaccination Period will be performed using the approach described by Follmann et al [15].

9.4.10 Safety Analyses

9.4.10.1 Reactogenicity

Reactogenicity will be measured with solicited local AEs (pain, erythema/redness, induration and swelling) and systemic AEs (fever, nausea/vomiting, diarrhea, headache, fatigue and myalgia) collected in the eCRF. The number and percentage of participants who had solicited local AEs and systemic AEs within 7 days after the first and second

vaccinations will be summarized by intervention group. These events will be tabulated by type of reactions, severity grade and onset.

All safety analyses will be performed on the Safety Analysis Set.

9.4.10.2 Adverse Events

Adverse Events will be classified by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals and Human Use (ICH).

A treatment-emergent adverse event (TEAE) is defined as an AE occurring after the first dose of study intervention. Of the AE reported in the eCRF, TEAE is used for the safety analysis.

The number and percentage of participants with TEAEs will be summarized by intervention group.

The number of participants with at least one TEAE leading to death, other serious TEAEs, MAAEs, AESIs, and discontinuation of study intervention will be similarly summarized. Treatment-related AEs will be summarized in the same manner as TEAEs. Treatment-related AEs will be defined as AEs considered as "related" to the study intervention.

A summary of TEAEs by MedDRA SOC and PT will be provided by intervention group and by intervention period, showing the number and percentage of participants with AEs. In addition, data will be summarized by severity, time to onset, and duration. Treatment-related AEs will be summarized in the same manner.

All AEs, including those occurring prior to the first dose of study intervention, will be listed.

9.4.10.3 Vital Signs

Summary statistics for vital signs and change from baseline at each scheduled time point will be presented by intervention group and by intervention period. The baseline will be the last measurement obtained prior to study intervention (immediately prior to vaccination).

9.5 Interim Analyses

The primary efficacy endpoint will be formally assessed by the independent data monitoring committee (IDMC) at 3 time points during the Initial Vaccination Period, giving two unblinded interim analyses and a primary analysis. The interim analyses are planned at 50% (33 cases) and 75% (50 cases) of the total target cases (66 cases). The primary objective of the interim analyses is for early detection of reliable evidence that VE is above 30%. The Lan-DeMets O'Brien-Fleming approximation alpha-spending function is used to control the overall type I error at one-sided 0.025 over the interim

analyses and the primary analysis. The interim analyses will be performed by an unblinded Biostatistics and Programming team and reviewed by the IDMC that will make recommendations with regard to the continuation of the trial. Regardless of the outcomes at either interim analysis or the final primary analysis, the study will remain blinded at the participant level for study site personnel and study participants until the end of the study. There will be an unblinded biostatistician and programmer isolated from study personnel. They will complete these analyses independent of study team and sponsor. A separate Statistical Analysis Plan will include a detailed description of the responsibilities of the unblinded statistician and the communication plan with the IDMC.

9.6 Independent Data Monitoring Committee (IDMC)

For details on IDMC, refer to Section 10.1.5.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated. Competent authority notification, review and approval may be required as appropriate according to local country requirements.
- Any amendments to the protocol will require Competent authority and/or IRB/IEC approval (as appropriate) before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- For studies to be submitted as part of an EU marketing authorization application (MAA), the sponsor will select a Clinical Study Report (CSR) Coordinating Investigator who will sign the CSR.
- The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

The information on financial disclosure for investigators will be addressed in a separate agreement between the sponsor and the investigator.

10.1.3 Informed Consent Process

- The investigator or his/her representative must explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date that written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant directly identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants' personal data must be processed or transferred with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place.

10.1.5 Committees Structure

Independent Data Monitoring Committee (IDMC)

The IDMC will be established to review unblinded data, including both safety and cases of COVID-19 at regular intervals, at 2 planned interim analyses and at a primary analysis during the Initial Vaccination Period. Committee membership responsibilities, authorities, and procedures will be documented in the IDMC charter.

At the interim analyses, the IDMC will review the interim analysis results and make recommendations based on the evaluation of the early efficacy (Section 9.5).

All RT-PCR-positive COVID-19 cases during the study will be periodically reviewed by the IDMC in terms of potential vaccine-associated enhanced disease (VAED). Ad hoc review may be performed further to the occurrence of any vaccine-related SAE, or at request of the sponsor's medical monitor or designee. The principal investigator and sponsor's study responsible physician will inform the IDMC of any AE of concern.

10.1.6 Dissemination of Clinical Study Data

The sponsor will disclose information on this clinical study and the summary of the study results when they are available on the following websites according to the regulations of the countries in which the study is conducted.

Clinicaltrial.gov: http://www.clinicaltrials.gov

EU Clinical Trials Register: https://www.clinicaltrialsregister.eu/ctr-search/search

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on an eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The

investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Before unblinding the assignment of participants to the intervention groups at the time of the primary immunogenicity analysis, the drug accountability records and the used vials should be available for verification by the unblinded sponsor monitor, unblinded contract research organization (CRO), or designee at each monitoring visit as specified in the unblinded clinical monitoring plan.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

- Source documents provide evidence of the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Source documents are defined as original documents, data, and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial).

10.1.9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The sponsor/designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected, data have been collected, and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor’s procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

- All information regarding study intervention supplied by the sponsor to the investigator is privileged and confidential. The investigator agrees to use this information to accomplish the study and must not use it for other purposes without consent from the sponsor.

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.11 Study Administrative Structure

Sponsor:	Shionogi & Co., Ltd. 1-8, Doshomachi 3 chome, Chuo-ku, Osaka 541-0045, Japan
Sponsor contact information:	[redacted], Shionogi & Co., Ltd. 8F, Nissay Yodoyabashi East Bldg., 3-13, Imabashi 3-chome, Chuo-ku, Osaka 541-0042, Japan TEL: [redacted] FAX: [redacted]
Sponsor's Chief Medical Officer:	[redacted] Shionogi & Co., Ltd.
Medical Monitor:	[redacted] Shionogi & Co., Ltd.
Emergency contact:	[redacted] Shionogi & Co., Ltd. TEL: [redacted] FAX: [redacted] [redacted] Shionogi & Co., Ltd. TEL: [redacted] FAX: [redacted]
IWRS:	[redacted]
Contract Research Organization:	[redacted]
Laboratory for SARS-CoV-2 neutralizing antibody titer assay:	BML, Inc. 1-18-8, Koenji-minami, Suginami-ku, Tokyo 166-0003, Japan
Laboratory for virology test and anti-spike protein IgG antibody titer test:	LSI Medience Corporation 1-13-4, Uchikanda, Chiyoda-ku, Tokyo 101-8517, Japan

10.2 Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, blood chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Hospitalization for preplanned and elective procedures to treat a pre-existing condition that did not worsen after start of study will not be considered an AE, and therefore will not be considered an SAE despite requiring hospitalization. The exception is when the participant experiences another event which is fatal, is life-threatening, results in disability, leads to prolonged hospitalization or is considered to be medically significant during/following the procedure. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.2.3 Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator or subinvestigator will assess the intensity of solicited AEs reported during the study by referring to the FDA guidance [11] (see Section 10.4). However, if the participant died due to a solicited AE, this event will be of Grade 5 severity.

The intensity of each non-solicited AE and SAE will be assessed and classified into one of the following 5 categories:

Grade refers to the intensity of the AE. CTCAE Version 5.0 defines Grade 1 to 5 according to the following principles and describes the intensity of each AE individually:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

A semicolon (;) indicates "or" within the description of grade.

Activities of Daily Living (ADL)

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- The relationship of an event to the study drug will be determined by the investigator or subinvestigator according to the following criteria:
  - Related: An AE which can be reasonably explained as having been caused by the study drug. For example, the occurrence of the AE can be explained by any of the following: a pharmacological effect of the study drug (eg, a similar event had been reported previously); an increase/decrease of the dose affects the occurrence or seriousness of the AE; or all other causative factors (eg, medical history,

concomitant medication etc.) can be ruled out after careful analysis of sufficient information.

- Not related: An AE which cannot be reasonably explained as having been caused by the study drug.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- The investigator should provide rationale for the causality assessment in the Medical Comment field in EDC or if reporting via paper, the rationale for causality should be provided in the narrative section of paper SAE form.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor or CRO. However, **it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or CRO.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or CRO with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will report any updated SAE data to the sponsor or CRO within 24 hours of receipt of the information.

10.2.4 Reporting of SAEs

All SAEs must be reported to the sponsor or CRO in detail via EDC within 24 hours from the time point when the investigator first becomes aware of the SAE.

SAE Reporting to sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to sponsor will be EDC.
- If EDC is unavailable, then the site will use the paper SAE Form (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after EDC has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the sponsor by telephone.
- Contacts for SAE reporting are indicated below.

SAE Reporting to sponsor via Paper Form

- If EDC is unavailable, then the site will use the paper SAE Form in order to report the event within 24 hours.
- E-mail transmission is the preferred method to transmit this information to the sponsor.
- The investigator will complete the paper SAE Form, date, sign, and scan the Form to PDF file.
- The PDF file will be sent to safetyinfo@shionogi.co.jp.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented tubal ligation
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than a single FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) [c] • Bilateral tubal occlusion • Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable • Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable • Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
Effective Methods[d] That Are Not Considered Highly Effective Failure rate of ≥ 1% per year when used consistently and correctly.
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide[e] • Cervical cap, diaphragm, or sponge with spermicide

- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
d Considered effective, but not highly effective - failure rate of ≥ 1% per year.
e Male condom and female condom should not be used together (due to risk of failure from friction).

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.

Collection of Pregnancy Information

Male Participants whose partners become pregnant

- If the investigator recognizes that a female partner of any male participants becomes pregnant from the first dose of study intervention through at least 90 days after the last dose of study intervention, the investigator will collect pregnancy information on the female partner.
- After obtaining the required written consent directly from the pregnant female partner of the male participant, the investigator will record pregnancy information on the appropriate form and report it to the sponsor within 24 hours of learning of the participant's partner's pregnancy. The female partner of the male participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the mother and the neonate, and the information will be forwarded to the sponsor. General, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant from the first dose of study intervention through at least 90 days after the last dose of study intervention. The initial information will be recorded on the appropriate form and reported to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.4 Appendix 4: Grading of Solicited Local and Systemic Adverse Events

US FDA guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [11]

Solicited Local AEs

	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema /Redness*	2.5–5 cm	5.1–10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration /Swelling**	2.5–5 cm and does not interfere with activity	5.1–10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Solicited Systemic AEs

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Fever (°C) (Oral) * (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Fever (°C) (Axillary) (°F)	37.5 – 37.9 99.5 – 100.3	38.0 – 38.4 100.4 – 101.1	38.5 – 39.5 101.2 – 103	> 39.5 > 103
Nausea /vomiting	No interference with activity or 1–2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2–3 loose stools or < 400 grams /24 hours	4–5 stools or 400 – 800 grams /24 hours	6 or more watery stools or > 800 grams /24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

* No recent hot or cold beverages or smoking.

10.5 Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Phase 3-4 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Phase 3-4 Liver Chemistry Stopping Criteria and Follow-up assessments

Liver Chemistry Stopping Criteria– Liver Stopping Event	
ALT or AST -absolute	ALT or AST ≥ 8 × ULN
ALT or AST Increase	ALT or AST ≥ 5 × ULN but < 8 × ULN persists for ≥ 2 weeks ALT or AST ≥ 3 × ULN but < 5 × ULN persists for ≥ 4 weeks
Bilirubin[a, b]	ALT or AST ≥ 3 × ULN **and** total bilirubin ≥ 2 × ULN (> 35% direct bilirubin)
INR[b]	ALT or AST ≥ 3 × ULN **and** international normalized ratio (INR) > 1.5, if INR measured
Cannot Monitor	ALT or AST ≥ 5 × ULN but < 8 × ULN and cannot be monitored weekly for ≥ 2 weeks ALT or AST ≥ 3 × ULN but < 5 × ULN and cannot be monitored weekly for ≥ 4 weeks
Symptomatic[c]	ALT or AST ≥ 3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions, Monitoring and Suggested Follow up Assessments	
Actions	**Follow up Assessments**
• **Immediately** discontinue study intervention. • Report the event to the sponsor within **24 hours.** • Complete the Liver Event Form and complete a serious adverse event (SAE) data collection tool if the event also met the criteria for an SAE.[b] • Perform follow-up assessments as described in the Follow Up Assessment column. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**).	• Viral hepatitis serology[d] • Obtain serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) • Fractionate bilirubin, if total bilirubin ≥ 2 × ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the eCRF as an AE. • Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs and other over-

MONITORING: **<u>If ALT or AST ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN or INR > 1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24 hours**. • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **<u>For all other criteria</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline. **RESTART/RECHALLENGE** • **Do not restart/rechallenge** participant with study intervention unless allowed per protocol and sponsor approval is granted.	the-counter medications) on the eCRF. • Record alcohol use on the Liver Event Form. **If ALT or AST ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN or INR > 1.5 obtain the following in addition to the assessments listed above:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct assay to access potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [17]. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease; complete the Liver Event Form. • Liver biopsy may be considered and discussed with local specialists if available for instance: – In participants when serology raises the possibility of autoimmune hepatitis (AIH) – In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention – In participants with acute or chronic atypical presentation: hepatic vascular disorder, chronic hepatitis fibrosis, micro vesicular statosis. • If liver biopsy is conducted, then complete the Liver Event Form.

a Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

b All events of ALT or AST ≥ 3 × ULN **and** total bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT or AST ≥ 3 × ULN **and** INR > 1.5 may indicate severe liver injury **and must be reported to sponsor in an expedited manner and as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.

c New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

d Includes: hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [18].

Phase 3-4 Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT or AST ≥ 5 × ULN and < 8 × ULN **and** total bilirubin < 2 × ULN or INR < 1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT or AST ≥ 3 × ULN and < 5 × ULN **and** total bilirubin < 2 × ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the sponsor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin) until the abnormalities resolve, stabilize, or return to baseline. • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 7.1. • If ALT or AST decreases from ALT or AST ≥ 5 × ULN and < 8 × ULN to ≥ 3 × ULN but < 5 × ULN, continue to monitor liver chemistries weekly. • If after 4 weeks of monitoring, ALT or AST < 3 × ULN and total bilirubin < 2 × ULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline.

10.6 Appendix 6: List of AESIs

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: - IgA nephropathy.

- 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.	- 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.

10.7 Appendix 7: Abbreviations and Acronyms

ACE2	angiotensin-converting enzyme 2
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BEVS	baculovirus expression vector system
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	chemiluminescence enzyme immunoassay
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
ECG	electrocardiogram/electrocardiography
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture system
ELISA	enzyme-linked immunosorbent assay
ER	emergency room
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
GMFR	geometric fold rise
GMT	geometric mean titer
HBsAg	hepatitis B surface antigen
HIPAA	Health Information Portability and Accountability Act

HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IDMC	independent data monitoring committee
IEC	institutional ethics committee
IgG	immunoglobulin G
IMP	investigational medicinal product
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LDH	lactate dehydrogenase
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NAb	neutralizing antibody
NIMP	non-investigational medicinal product
N-protein	SARS-CoV-2 nucleocapsid protein
PCR	polymerase chain reaction
PPS	per-protocol set
RNA	ribonucleic acid
RT-PCR	real-time polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SD	standard deviation
SoA	schedule of assessments
SpO_2	peripheral capillary oxygen saturation
S-protein	SARS-CoV-2 spike protein
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United State of America
VE	vaccine efficacy
WHO	World Health Organization

WHODD	World Health Organization Drug Dictionary
WOCBP	women of child-bearing potential

10.8 Appendix 8: Investigator's Signature

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
Date of Original:	28 Oct 2021
Date of Latest Version:	8 Jul 2022

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

11. REFERENCES

1. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/ Accessed 7 July 2022.
2. Cevik M, Kuppalli K, Kindrachuk J, Peiris M. Virology, transmission, and pathogenesis of SARS-CoV-2. BMJ 2020;371:m3862.
3. Benton DJ, Wrobel AG, Xu P, et al. Receptor binding and priming of the spike protein of SARS-CoV-2 for membrane fusion. Nature 2020;588:327-30.
4. Bozkurt B, Kamat I, Hotez PJ. Myocarditis With COVID-19 mRNA Vaccines. Circulation 2021;144:471-84.
5. Sharifian-Dorche M, Bahmanyar M, Sharifian-Dorche A, et al. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review. J Neurol Sci 2021;428:117607.
6. Felberbaum RS. The baculovirus expression vector system: A commercial manufacturing platform for viral vaccines and gene therapy vectors. Biotechnol J 2015;10(5):702-14.
7. S-268019 Investigator's Brochure
8. Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. Am J Epidemiol 2004; 159 (7):702-6.
9. Guidance for Industry. Development and Licensure of Vaccines to Prevent COVID-19. US Food and Drug Administration. June 2020.
10. CDC. (Centers for Disease Control and Prevention). Coronavirus Disease 2019 (COVID-19), Symptoms of Coronavirus. https://www.cdc.gov/coronavirus/2019-ncov/symptomstesting/symptoms.html. Published 2020.
11. Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. US Food and Drug Administration. September 2007.
12. Goepfert PA, Fu B, Chabanon A-L, et al. Safety and immunogenicity of SARS-CoV-2 recombinant protein vaccine formulations in healthy adults: interim results of a randomised, placebo-controlled, phase 1–2, dose-ranging study. Lancet Infect Dis 2021, Published online, April 19, 2021.
13. Tavares Da Silva F, De Keyser F, Lambert PH, et al. Optimal approaches to data collection and analysis of potential immune mediated disorders in clinical trials of new vaccines. Vaccine 2013;31:1870-6.
14. Chan ISF, Bohidar NR. Exact power and sample size for vaccine efficacy studies. Commun Statist-Theory Meth 1998: 27(6); 1305-22.
15. Follmann D, Fintzai J, Fay MP, et al. Assessing Durability of Vaccine Effect Following Blinded Crossover in COVID-19 Vaccine Efficacy Trials. medRxiv 2020 Dec 14 Preprint.

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

17. James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-84.

18. Le Gal F, Gordien E, Affolabi D, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol 2005;43(5):2363-9.

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