2. SYNOPSIS

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Name of Active Ingredient: S-217622	Page	e:	
Study Title: A Phase 2/3 Study of S-217622 in Par	rticipa	ants Infected with SA	ARS-CoV-2
Investigators and Study Centers: The in Japan in Phase 2a Part.	his wa	as a multicenter stud	y conducted at 56 sites
Publication (reference): Not application	ble		
Studied Period: From 28 Sep 2021 to participants in Phase 2a Part)	o 27 J	an 2022 (Last observ	vation date of the last
Phase of Development: Phase 2/3			
Phase 2a Part; Participants with Mild/ Infection Objectives	Mode		tic SARS-CoV-2
Primary			
Common to participants with mild/moderate syndrome coronavirus 2 (SARS-CoV-2) inf			e acute respiratory
• To investigate the antiviral effect of 5-c administration of S-217622 in participa with SARS-CoV-2 infection.		• Change from base titer at each time p	line in SARS-CoV-2 viral point
Secondary			
Common to participants with mild/moderate			
• To investigate the antiviral effect of 5-c administration of S-217622 other than t		• The following end CoV-2 viral titer	points concerning SARS-
primary endpoint in participants with SARS-CoV-2 infection.			t negative SARS-CoV-2
			e SARS-CoV-2 viral cutive time points
		viral titer	ed negative SARS-CoV-2
		SARS-CoV-2 v	articipants with positive iral titer at each time point
		 Relative change 	iral titer at each time point rate from baseline in iral titer at each time point

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 To investigate the effect in preventing aggravation following 5-day administr of S-217622 in participants with SARS CoV-2 infection. 	SARS-CoV-2 The following entranscription pole (RT-PCR) testin Time to the find Time to negating consecutive Time to sustance results Proportion of former Amount of SA each time point Amount of SA each time point Relative chance amount of SA each time point Relative chance amount of SA each time point Relative chance amount of SA each time point AUC of chance CoV-2 viral Find Proportion of part following or hig Ordinal Scale ard dose of study interscores Symptomatic, (Score 1) Symptomatic, (Score 3) Hospitalized, (≤ 5 L/min) (State 1) Hospitalized, (≥ 5 L/min) (State 2) Autor (State 2) Hospitalized, (≥ 5 L/min) (State 2) Autor (State	ndpoints concerning reverse lymerase chain reaction og (nasopharyngeal swabs) rst negative RT-PCR result tive RT-PCR results at time points ined negative RT-PCR participants with positive It at each time point ARS-CoV-2 viral RNA at nt baseline in the amount of viral RNA at each time ge rate from baseline in the RS-CoV-2 viral RNA at nt ge in the amount of SARS- RNA articipants with the her scores on the 8-Point at the time from the first tervention to reach the , no limitation of activities no oxygen therapy Score 4) with oxygen therapy Score 5) with ventilation (Score 6)

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5-217622			
	•	• Saturation of perc at each time point	cutaneous oxygen (SpO ₂)
• To investigate quality of life (QOL) following 5-day administration of S-21 in participants with SARS-CoV-2 infe		• Change from base 5 dimensions 5-le	
• To confirm the pharmacokinetics (PK) following 5-day administration of S-21 in participants with SARS-CoV-2 infe	17622	Plasma concentra (Days 2, 6)	tion of S-217622
• To investigate the safety and tolerabili following 5-day administration of S-21 in participants with SARS-CoV-2 infe	17622		•
Participants with mild/moderate SARS-Co	V-2 infect	tion ^a	
• To investigate the effect in improving clinical symptoms following 5-day administration of S-217622 in participants with mild/moderate SARS-CoV-2 infection.		disease 2019 (COTime to first imprsymptoms (durati	rovement of coronavirus WID-19) symptoms ^{b, c} rovement of COVID-19 on of recovery, 72 hours
			on of recovery, 120 hours
	•		ovement of each
	•	e	eline in the total score of toms at each time point ^b
	•	r roportion or pui	COVID-19 symptoms and
	•	1 1	ticipants with taste disorder at each time point
			n of fever (< 37.0°C)
Participants with asymptomatic SARS-CoV			
• To investigate the preventive effect of administration of S-217622 in particip	ants	 Proportion of part of COVID-19 syr 	ticipants with development nptoms ^{e, f}
with asymptomatic SARS-CoV-2 infe	ction.		ticipants with development nptoms with fever
Exploratory			

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• To evaluate immunity in participants w SARS-CoV-2 infection.			iter for SARS-CoV-2 ody titer (Days 1, 28)
• To evaluate the effect of 5-day administration of S-217622 on aggravat markers in participants with SARS-Cov infection.	ion m	hange from base arkers ^g	line in aggravation
• To investigate the effect on post-acute COVID-19 syndrome following 5-day administration of S-217622 in participa with SARS-CoV-2 infection.	С		icipants with post-acute ome at each time point

Phase 2b Part; Participants with Mild/Moderate SARS-CoV-2 Infection

Objectives	Endpoints	
Primary		
• To compare the effect in improving clinical symptoms following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection, based on the time-weighted average change in total score of 12 COVID-19 symptoms from initiation of administration (Day 1) up to 120 hours (Day 6).	• Time-weighted average change in total score of 12 COVID-19 symptoms from initiation of administration (Day 1) up to 120 hours (Day 6) ^b	
• To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in participants with SARS- CoV-2 infection, based on the change from baseline on Day 4 in SARS-CoV-2 viral titer.	• Change from baseline on Day 4 in SARS- CoV-2 viral titer	
Secondary		
• To compare the effect in improving clinical symptoms following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	 Time to first improvement of COVID-19 symptoms^{b, c} Time to first improvement of COVID-19 symptoms (duration of recovery, 72 hours [3 days] or longer)^{b, c, d} Time to first improvement of COVID-19 	
	 symptoms (duration of recovery, 120 hours [5 days] or longer)^{b, c, d} Time to first improvement of each COVID-19 symptom^{b, c} 	

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S-217622		
• To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-Cov infection.	 COVID-19 symption Proportion of partising properties of the cash symptom at Proportion of partial disorder or smell point Time to resolution The following end SARS-CoV-2 vira Time to the first viral titer Time to negative titers at 2 consections Time to sustain a viral titer Proportion of partial titer Proportion of partial titer SARS-CoV-2 vira Time to sustain a viral titer Proportion of partial titer Relative change sARS-CoV-2 v Change from ba viral titer at each viral titer Relative change sARS-CoV-2 v AUC of change titer The following end RT-PCR testing (r Time to sustain a results Proportion of partial tites Proportion of partial tites 	20VID-19 symptoms and each time point ^{b, c} ticipants with taste disorder at each time a of fever (< 37.0°C) points concerning 1 titer a negative SARS-CoV-2 e SARS-CoV-2 viral cutive time points ed negative SARS-CoV-2 articipants with positive iral titer at each time point iral titer at each time point seline in SARS-CoV-2 h time point a rate from baseline in iral titer at each time point in SARS-CoV-2 viral points concerning asopharyngeal swabs) a negative RT-PCR result e RT-PCR results at

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 To compare the effect to prevent aggravation following 5-day administr of S-217622 with that of placebo in participants with SARS-CoV-2 infecti 		 SARS-CoV-2 v point Relative change amount of SAR each time point AUC of change CoV-2 viral RN Proportion of part following or highe Ordinal Scale and dose of study inter scores Symptomatic, n (Score 1) Symptomatic, ni (Score 2) Hospitalized, no (Score 3) Hospitalized, w (< 5 L/min) (Sc Hospitalized, w (≥ 5 L/min) (Sc Hospitalized, w Death (Score 7) SpO₂ at each time 	in the amount of SARS- IA icipants with the er scores on the 8-Point the time from the first rvention to reach the to limitation of activities imitation of activities to oxygen therapy or 4) ith oxygen therapy ore 5) ith ventilation (Score 6) point
 To compare QOL following 5-day administration of S-217622 with that of placebo in participants with SARS-Co infection. 		Change from base	line in EQ-5D-5L
• To confirm the PK following 5-day administration of S-217622 in particip with SARS-CoV-2 infection.	oants	• S-217622: Plasma	concentration (Days 2, 6)
• To compare the safety and tolerability following 5-day administration of S-2 with those of placebo in participants w SARS-CoV-2 infection.	17622		ests, and vital signs blood pressure, pulse rate, te)
Exploratory			
• To analyse SARS-CoV-2 lineage for participants with SARS-CoV-2 infecti	ion.	• Spike gene sequer	nce of SARS-CoV-2

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S-217622			
• To perform polymorphism analysis of 3 protease (nsp5) for participants with SA CoV-2 infection.		Gene sequence of SARS-CoV-2	3CL protease (nsp5) of
• To evaluate the amino acid substitution: 3CL protease (nsp5) following 5-day administration of S-217622 in participa with SARS-CoV-2 infection.			3CL protease (nsp5) itervention administration
• To evaluate the antiviral activity of S-217622 against SARS-CoV-2 in participants' specimen.			ective concentration (EC ₅₀) ARS-CoV-2 isolated from
• To evaluate immunity in participants w SARS-CoV-2 infection.	ith		iter for SARS-CoV-2 ody titer (Days 1, 28)
• To evaluate the effect of 5-day administration of S-217622 on aggravat markers in participants with SARS-Cov infection.		• Change from base markers ^g	line in aggravation
• To investigate the effect on post-acute COVID-19 syndrome following 5-day administration of S-217622 in participa with SARS-CoV-2 infection.	nts		icipants with post-acute ome at each time point

Phase 3 Part, Participants with Mild/Moderate SARS-CoV-2 Infection

Objectives	Endpoints
Primary	
• To compare the effect in improving clip symptoms following 5-day administrat of S-217622 with that of placebo in participants with mild/moderate SARS-CoV-2 infection who have at lea 3 moderate symptoms, based on the tin improvement of COVID-19 symptoms	ast ne to
Key Secondary	
• To compare the antiviral effect of 5-day administration of S-217622 with that o placebo in participants with SARS-Cov infection, based on time to the first neg SARS-CoV-2 viral titer.	f titer V-2
• To compare the effect in improving clip symptoms following 5-day administrat	1

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of S-217622 with that of placebo in participants with mild/moderate SARS-CoV-2 infection who have at lea 1 moderate symptoms, based on the tim improvement of COVID-19 symptoms.	le to	
• To compare the effect in improving clir	nical • Time to first imp	rovement of COVID-19
symptoms following 5-day administrati of S-217622 with that of placebo in participants with SARS-CoV-2 infectio	 on symptoms (durat [3 days] or longe n. Time to first imp symptoms (durat [5 days] or longe Time to first imp COVID-19 symp Time-weighted a score of 12 COV initiation of admin 120 hours (Day 6 Change from bas COVID-19 symp Proportion of par improvement of each symptom at Proportion of par disorder or smell 	rovement of COVID-19 ion of recovery, 120 hours r) ^{b, c, d} rovement of each otom ^{b, c} verage change in total ID-19 symptoms from inistration (Day 1) up to 5) ^b eline in total score of otoms at each time point ^b
• To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV infection.	 The following en SARS-CoV-2 vin SARS-CoV-2 vin titers at 2 conditions at 2 conditing at 2 conditions at 2 conditions at 2 conditions at 2 conditi	dpoints concerning ral titer ative SARS-CoV-2 viral nsecutive time points ained negative SARS-

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 To compare the effect to prevent aggravation following 5-day administra of S-217622 with that of placebo in participants with SARS-CoV-2 infection 	 SARS-Colpoint AUC of chatter The following RT-PCR testin Time to that result Time to near 2 consecut Time to near 2 consecut Time to suresults Proportion RT-PCR results Proportion RT-PCR result Change for SARS-Colpoint Relative clatter of the amount at each time result at each time resu	bom baseline in the amount of V-2 viral RNA at each time hange rate from baseline in t of SARS-CoV-2 viral RNA

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S-217622	1 450.	
 To compare QOL following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV infection. To confirm the PK following 5-day administration of S-217622 in participa with SARS-CoV-2 infection. To compare the safety and tolerability following 5-day administration of S-21 with those of placebo in participants wi SARS-CoV-2 infection. 	 Death (Score SpO₂ at each tim Change from bas 7-2 S-217622: Plasm AEs, laboratory to (systolic/diastolic) 	e point beline in EQ-5D-5L na concentration (Days 2, 6) tests, and vital signs c blood pressure, pulse rate,
Exploratory		COADO O MO
 To analyse SARS-CoV-2 lineage for participants with SARS-CoV-2 infectio To perform polymorphism analysis of 3 protease (nsp5) for participants with SA CoV-2 infection. To evaluate the amino acid substitution 3CL protease (nsp5) following 5-day 	n. GCL Gene sequence o ARS- SARS-CoV-2 s in Gene sequence o	ence of SARS-CoV-2 f 3CL protease (nsp5) of f 3CL protease (nsp5) intervention administration
 administration of S-217622 in participal with SARS-CoV-2 infection. To evaluate the antiviral activity of S-217622 against SARS-CoV-2 in participant's specimen. To evaluate immunity in participants w SARS-CoV-2 infection. To evaluate the effect of 5-day 	nts • EC ₅₀ of S-217622 from baseline sar ith • Geometric mean neutralizing antil • Change from bas	2 on SARS-CoV-2 isolated
 administration of S-217622 on aggravation markers in participants with SARS-CoV infection. To investigate the effect on post-acute COVID-19 syndrome following 5-day administration of S-217622 in participation with SARS-CoV-2 infection. 	 Proportion of par COVID-19 syndr 	rticipants with post-acute rome at each time point

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Phase 2b/3 Part; Participants with Asy Infection	mptomatic/Mild Symp	otoms Only SARS-CoV-2
Objectives		Endpoints
 Primary To compare the effect of 5-day administration of S-217622 on preventi development or worsening of symptoms with that of placebo in participants with SARS-CoV-2 infection. 	ng development/w s symptoms ^{e, h}	participants with vorsening of COVID-19
 Key secondary To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV infection, based on time to the first nega SARS-CoV-2 viral titer. 	viral titer	st negative SARS-CoV-2
 Other secondary To investigate the preventive effect of 5 administration of S-217622 in participa with asymptomatic SARS-CoV-2 infect To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV infection. 	nts of COVID-19 s ition. Proportion of p of COVID-19 s $(\geq 37.0^{\circ}C)^{\circ}$. f The following CoV-2 viral tite 7-2 - Time to ne titers at 2 o - Time to su CoV-2 viral - Proportion SARS-Compoint - SARS-Compoint - Change from viral titers at - Relative cl	endpoints concerning SARS- er egative SARS-CoV-2 viral consecutive time points ustained negative SARS-

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 To compare the effect to prevent aggravation following 5-day administr of S-217622 with that of placebo in participants with SARS-CoV-2 infection 		titer The following end RT-PCR testing (f - Time to the fire result - Time to nega 2 consecutive - Time to sustare results - Proportion of RT-PCR result - Amount of S. each time point - Change from SARS-CoV-2 point - Relative chart the amount of at each time point - AUC of chant SARS-CoV-2 Proportion of part following or high Ordinal Scale and of study intervent - Symptomatic (Score 1) - Symptomatic (Score 3) - Hospitalized, (< 5 L/min) (- Hospitalized, (< 5 L/min) (ined negative RT-PCR participants with positive It at each time point ARS-CoV-2 viral RNA at int baseline in the amount of 2 viral RNA at each time age rate from baseline in f SARS-CoV-2 viral RNA opint ge in the amount of 2 viral RNA icipants with the er scores on the 8-Point time from the first dose ion to reach the scores , no limitation of activities , limitation of activities no oxygen therapy with oxygen therapy Score 4) with oxygen therapy Score 5) with ventilation (Score 6) 7)

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S-217622		
 To compare QOL following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV- infection. 	-2 • Change from base	line in EQ-5D-5L
 To confirm the PK following 5-day administration of S-217622 in participan with SARS-CoV-2 infection. 		concentration (Days 2, 6)
• To compare the safety and tolerability following 5-day administration of S-217 with those of placebo in participants with SARS-CoV-2 infection.	622 (systolic/diastolic	ests, and vital signs blood pressure, pulse rate, re)
Exploratory		
 To analyse SARS-CoV-2 lineage for participants with SARS-CoV-2 infection To perform polymorphism analysis of 30 protease (nsp5) for participants with SAI CoV-2 infection. To evaluate the amino acid substitutions 3CL protease (nsp5) following 5-day 	 n. CL Gene sequence of SARS-CoV-2 in Gene sequence of 	ace of SARS-CoV-2 3CL protease (nsp5) of 3CL protease (nsp5) tervention administration
 administration of S-217622 in participan with SARS-CoV-2 infection. To evaluate the antiviral activity of S- 217622 against SARS-CoV-2 in participant's specimen. 	• EC ₅₀ of S-217622 from baseline sam	on SARS-CoV-2 isolated
 To evaluate immunity in participants with SARS-CoV-2 infection. To evaluate the effect of 5-day administration of S-217622 on aggravati markers in participants with SARS-CoV infection. 	 neutralizing antibo Change from base markers^g 	iter for SARS-CoV-2 ody titer (Days 1, 28) line in aggravation
 To investigate the effect on post-acute COVID-19 syndrome following 5-day administration of S-217622 in participan with SARS-CoV-2 infection. 	COVID-19 syndro	icipants with post-acute ome at each time point
a Participants with mild/moderate SARS-CoV-2 criterion #2 to #4 in Section 9.3.1.1 but did not participants with asymptomatic SARS-CoV-2 criterion #2 and #3 in Section Error! Reference criterion #1 to #5 in Section Error! Reference	t meet exclusion criterion $\#1$ to $\#1$ infection were defined as particip ce source not found. 9.3.1.2 but of	5 in Section 9.3.2.1; bants who met inclusion
b The following 12 symptoms were evaluated: lo		body aches, headache, chills

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	or shivering, feeling hot or feverish, stuffy or breathing), nausea, vomiting, and diarrhea.	runny nose, sore throat, cough, sh	ortness of breath (difficulty
c	The 12 symptoms of COVID-19 were evalua Severe). The time to improvement of COVID intervention to when all of the symptoms met	0-19 symptoms was defined as the	
	 Pre-existing symptoms that were present have worsened at baseline (pre-treatmen moderate or better, or moderate symptor 	t examination): Severe symptoms	at baseline has improved to
	 Pre-existing symptoms that were present to have worsened at baseline (pre-treatm severe or improved, or moderate symptom) 	nent examination): Severe symptor	ns at baseline has remained
	 Symptoms other than the above (Sympto after baseline [pre-treatment examination 		
d	As for the definition of the time to improvement of COVID-19 symptoms described in c, the duration of improvement read as 72 hours or longer, or 120 hours or longer.		
e	A total of 14 symptoms were evaluated: taste low energy or tiredness, muscle or body ache runny nose, sore throat, cough, shortness of b	s, headache, chills or shivering, fe	eling hot or feverish, stuffy or
f	Of the 14 symptoms in COVID-19, taste diso 2 (0, The same as usual; 1, Less than usual; 2 evaluated on a 4-point scale of 0 to 3 (0, Non development of any COVID-19 symptoms we the following criteria.	, No sense of smell/taste). The oth e; 1, Mild; 2, Moderate; 3, Severe	er 12 symptoms were). Participants with
	 The scores for taste disorder or smell dis usual) or 2 (No sense of smell/taste). 	sorder has worsened from 0 (The s	ame as usual) to 1 (Less than
	 Feeling hot or feverish, cough, or shortn has worsened to mild or worse, mild syn moderate symptoms at baseline has wors baseline were excluded from the onset ju 	nptoms at baseline has worsened to sened to severe on any of the symp	o moderate or worse, or otoms (severe symptoms at
	 Low energy or tiredness, muscle or body throat, nausea, vomiting, or diarrhea: Se symptoms at baseline has worsened to n worsened to severe on 2 or more sympto excluded from the onset judgement of C 	verity of none at baseline has wors noderate or worse, or moderate syr oms at the same point (severe symp	sened to mild or worse, mild nptoms at baseline has
g	Aggravation markers included platelet count, LDH, albumin, CRP, CK, PT-INR, IL-6, IFN		
h	Of the 14 symptoms in COVID-19, taste diso (0, The same as usual; 1, Less than usual; 2, 1 on a 4-point scale of 0 to 3 (0, None; 1, Mild; development/worsening of any COVID-19 sy any of the following criteria.	No sense of smell/taste). The other ; 2, Moderate; 3, Severe). Participa	12 symptoms are evaluated ints with
	 The scores for taste disorder or smell dis or 2 (No sense of smell/taste), or from 1 		

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score of 2 [No sense of smell/taste] was symptoms).	excluded from the onset/worsenin	g judgement of COVID-19
 Feeling hot or feverish, cough, shortness worsen to mild or worse, mild symptoms symptoms at baseline worsen to severe of from the onset/worsening judgement of of 	s at baseline worsen to moderate o on either symptom (severe sympton	r worse, or moderate
 Low energy or tiredness, muscle or body throat, nausea, vomiting, and diarrhea: S symptoms at baseline worsen to moderat which were maintained for 24 hours on 2 baseline were excluded from the onset/w 	everity of none at baseline worsen te or worse, or moderate symptom 2 or more symptoms at the same p	s to mild or worse, mild s at baseline worsen to severe oint (severe symptoms at
i Participants who have one or two moderate (0 according to the master protocol.	COVID-19 score: 2) symptoms ma	y have been included
Methodology:		

This study consisted of four parts: Phase 2a Part enrolling participants with mild/moderate or asymptomatic SARS-CoV-2 infection, Phase 2b Part and Phase 3 Part enrolling participants with mild/moderate SARS-CoV-2 infection (cohort A to evaluate time to improvement), and Phase 2b/3 Part enrolling participants with asymptomatic/mild symptoms only SARS-CoV-2 infection (cohort B to evaluate development/worsening). This study was a multicenter, randomized, double-blind, placebo-controlled study. The participants were at home, at accommodation facilities, or in a hospital.

In each part, eligible participants were randomly assigned to S-217622 125 mg group, S-217622 250 mg group, or placebo group.

- S-217622 125 mg group (5-day administration once-daily): As a loading dose, S-217622 375 mg was administrated only at the first study intervention. Thereafter, S-217622 125 mg was administered on Days 2 to 5.
- S-217622 250 mg group (5-day administration once-daily): As a loading dose, S-217622 750 mg was administrated only at the first study intervention. Thereafter, S-217622 250 mg was administered on Days 2 to 5.
- Placebo group Placebo was administered once daily for 5 days.

Each Part consisted of the intervention period (Days 1 to 5), the follow-up period (Days 6 to 28), and the exploratory period (Days 29 to 337), which was common for all Parts. Participants were considered to have completed the study if he/she had

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completed the follow-up period. Only participants who agreed to participate in the exploratory period were evaluated in the period.

In this study, the Data and Safety Monitoring Board was established for the purpose of third-party evaluation of safety throughout the study period. The Independent Data Monitoring Committee (IDMC) will be established for the interim analyses of the primary endpoint and the key secondary endpoint of each of Phase 3 Part and Phase 2b/3 Part for the purpose of decision on stopping the study for efficacy reasons. It will control such unblinded information as the key codes and the results of analysis which may have an impact on the conduct or evaluation of Phase 3 Part and Phase 2b/3 Part.

Number of Participants (Planned and Analyzed):

Planned:

For Phase 2a Part, 69 eligible participants with mild/moderate or asymptomatic SARS-CoV-2 infection were to be enrolled in 3 groups (23 participants/group). The number of participants by condition (mild/moderate or asymptomatic) in each group was not pre-defined.

For Phase 2b Part, 435 eligible participants with mild/moderate SARS-CoV-2 infection who have at least 1 moderate symptom are enrolled in 3 groups (145 participants/group).

For Phase 3 Part, 1260 eligible participants with mild/moderate SARS-CoV-2 infection who have at least 3 moderate symptoms will be enrolled in 3 groups (420 participants/group). In the case no interim analysis is performed for the purpose of decision on stopping the study for efficacy reasons, 1215 eligible participants will be randomly assigned to each of these intervention groups (405 participants/group).

For Phase 2b/3 Part, 600 eligible participants with asymptomatic/mild symptoms only SARS-CoV-2 infection will be enrolled in 3 groups (200 participants/group). In the case no interim analysis is performed for the purpose of decision on stopping the study for efficacy reasons, 570 eligible participants will be randomly assigned to each of these intervention groups (190 participants/group).

Randomized (Phase 2a Part):

Analyzed for efficacy (Phase 2a Part):

- 1. Participants with mild/moderate SARS-CoV-2 infection
 - Intention-to-treat (ITT) population:
 40 participants (14 in the S-217622 125 mg group, 12 in the S-217622 250 mg group, and 14 in the placebo group)

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 Modified intention-to-treat (m 37 participants (13, 12, and 1) Per protocol set (PPS): 33 participants (13, 9, and 11) 	2)	
2. Participants with asymptomatic S	SARS-CoV-2 infection	
• ITT population: 7 participants (2 in the S-217 group, and 3 in the placebo gr	00 1	ne S-217622 250 mg
 mITT population: 6 participants (2, 2, and 2) PPS: 7 participants (2, 2, and 2) 		
7 participants (2, 2, and 3)) .	
 Analyzed for safety (Phase 2a Part Safety analysis population 68 participants (21 in the S-2 group, and 24 in the placebo g 	17622 125 mg group, 23 i	in the S-217622 250 mg
Diagnosis and Main Criteria for In	iclusion:	
The inclusion and exclusion criteria 1. Inclusion criteria		8.
Common to participants with mild/m asymptomatic/mild symptoms only S	SARS-CoV-2 infection:	
• Male and female participants signing the informed consent.	•	rs of age, at the time of
 Participants who were diagnore before randomization. 	osed as SARS-CoV-2 posi	tive within 120 hours
• Participants under 20 years of	f age at the time of assent	had to weigh \ge 40 kg.
Participants with mild/moderate SAF Part, and Phase 3 Part):		× -
• Participants with a time from 14 symptoms of COVID-19 c	occurred) to randomization	n of \leq 120 hours.
 Participants who had at least symptom among the 12 COV symptoms present prior to CO 	TD-19 symptoms at rando	· · · · · · · · · · · · · · · · · · ·

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pre-existing symptom	ad at least one moderate (COVI (symptoms present prior to CO d to have worsened at baseline:	
Participants who had r	ic SARS-CoV-2 infection only none of the COVID-19 symptom CoV-2 infection) within 2 week	ns (except symptoms
Participants with asymptomat 2b/3 Part only):	ic/mild symptoms only SARS-0	CoV-2 infection (Phase
symptom score: 2) or s	ot have any symptoms of mode severe out of the 12 symptoms of ks before randomization (exclu set).	due to COVID-19
2. Exclusion criteria		
• Participants with a Sp	O_2 during wakefulness of $\leq 93\%$	⁄₀ (room air)
• Participants who need	ed oxygen administration or a r	espirator
-	strongly suspected to have wor n within 48 hours after randomizestigator	• • •
1 1	ected active and systemic infect zation (excluding SARS-CoV-2	1 0
Test Product, Dose and Mod	le of Administration, Lot Nur	nber (Phase 2a Part):
Study Intervention Name	Packaging Lot No.	
S-217622 tablet 250 mg	Day1,	
S-217622 tablet 125 mg	Days 2 to 5,	
S-217622 tablet 250 mg or S- described in the Methodology	217622 tablet 125 mg was orall	y administered as
Duration of Treatment:		
Once daily for 5 days		

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Reference Therapy, Dose and Mode of Administration, Lot Number (Phase 2a Part):

Study Intervention Name Packaging Lot No.

S-217622 tablet Placebo-D Day1,

S-217622 tablet Placebo-B Days 2 to 5,

S-217622 tablet Placebo-D and/or S-217622 tablet Placebo-B was orally administered as described in the Methodology.

Criteria for Evaluation:

Efficacy Assessment:

1. Virologic Examination

The investigator or his/her designee took nasopharyngeal swab from participants. SARS-CoV-2 virus titer and viral amount of viral RNA were measured, whether the sample was positive or negative was determined by RT-PCR.

2. Participant Diary

Participants assessed their COVID-19 symptom scores and EQ-5D-5L, measured SpO_2 and temperature, and entered the results in the participant diary.

• COVID-19 Symptom Score

Of the 14 COVID-19 symptoms listed below, participants assessed taste disorder and smell disorder themselves using a 3-point scale of 0 to 2 (0, The same as usual; 1, Less than usual; 2, No sense of smell/taste) and the other 12 symptoms using a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe) according to the protocol-specified schedule.

- General symptoms: Low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, taste disorder, smell disorder
- Respiratory symptoms: Stuffy or runny nose, sore throat, cough, and shortness of breath (difficulty breathing)
- Gastrointestinal symptoms: Nausea, vomiting, and diarrhea
- SpO₂

Participants measured SpO₂ using a pulse oximeter according to the protocol-specified schedule.

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Body Temperature		
Participants measured axilla schedule.	ry temperature according t	o the protocol-specified
• EQ-5D-5L		
Participants assessed EQ-5D	0-5L according to the proto	col-specified schedule.
questionnaire and EQ Visua questionnaire assesses 5 par pain/discomfort, and anxiety scores assess the participant where the best state is 100 a	ameters (mobility, self-care //depression) on a 5-point s 's current health on a 20 cm	e, usual activities, scale. The EQ VAS
3. 8-Point Ordinal Scale		
The investigator/subinvestigator 8-Point Ordinal Scale of 0 to 7 a The scores on the 8-Point Ordin limitation of activities; 2) Symp no oxygen therapy; 4) Hospitali 5) Hospitalized, with oxygen the ventilation; and 7) Death.	according to the protocol-sp al Scale are 0) Asymptoma tomatic, limitation of activ zed, with oxygen therapy (pecified schedule. atic; 1) Symptomatic, no ities; 3) Hospitalized, < 5 L/min);
Other Assessments:		
Results of the following assessment study report.		ly from the clinical
 Biomarkers (aggravation ma SARS-CoV-2 lineage 	ukeis)	

- SARS-CoV-2 lineage
- Polymorphisms of 3CL Protease (nsp5)
- Proportion of amino acid substitution in 3CL protease (nsp5) gene
- Drug antiviral activity
- Immunity (SARS-CoV-2 neutralizing antibody titers)

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Safety Assessment:

Safety was assessed through physical examinations, laboratory tests, vital signs, and ECGs. All AEs/serious AEs (SAEs) were collected from the date of signing of the informed consent form (ICF)/assent through the end of follow-up period. The severity and seriousness of an event was determined by the investigator according to the protocol-specified definitions. The relationship of an event to the study intervention was determined by the investigator.

Pharmacokinetics Assessment:

For the measurement of plasma S-217622 concentrations, blood samples were collected on Days 2 and 6.

Statistical Methods:

Efficacy Analyses:

In general, efficacy analyses were performed for ITT population (Phase 2a Part), ITT1 population (Phase 2b Part), ITT2 population (Phase 3 Part, Phase 2b/3 Part), or mITT population, ie, ITT or ITT2 participants who had a positive SARS-CoV-2 viral titer at baseline (common for Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part). As for the primary endpoints of Phase 2a Part and Phase 2b Part, and the primary and key secondary endpoints of Phase 3 Part and Phase 2b/3 Part, only the primary analyses were to be performed based on the PPS instead of ITT, ITT1, and ITT2 population, respectively, and based on the PPS with positive SARS-CoV-2 viral titer at baseline instead of mITT population for Phase 2a Part.

Primary Endpoint in Phase 2a Part (Participants with Mild/Moderate or Asymptomatic SARS-CoV-2 infection)

The primary endpoint in Phase2a Part, ie, the change from baseline in SARS-CoV-2 viral titer at each time point, was defined as the absolute change from baseline in SARS-CoV-2 viral titer at each time point. Summary statistics for the change from baseline in SARS-CoV-2 viral titer at each time point were calculated using the mITT population for the participants with mild/moderate SARS-CoV-2 infection, the participants with asymptomatic SARS-CoV-2 infection, and the merged population separately. In addition, the van Elteren test was applied to the merged population of mild/moderate and asymptomatic SARS-CoV-2 infection for a pairwise comparison of SARS-CoV-2 viral titer at each time point between each S-217622 treatment group and the placebo group at a two-sided significance level of 0.05. As stratification factors for van Elteren test, the condition of SARS-CoV-2 infection (mild/moderate or

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asymptomatic) was used. No multiplicity adjustment was performed in these pairwise comparisons.

Primary Endpoint in Phase 2b Part (Participants with Mild/Moderate SARS-CoV-2 Infection)

The primary efficacy endpoints in participants with mild/moderate SARS-CoV-2 infection in Phase 2b Part are the time-weighted average change in total score of 12 COVID-19 symptoms from initiation of administration (Day 1) up to 120 hours (Day 6) and the change from baseline on Day 4 in SARS-CoV-2 viral titer.

As the primary analysis for this primary endpoint, pairwise comparison will be performed between each S-217622 intervention group and the placebo group, analysis of covariance will be applied with time-weighted average change as response, and by time from COVID-19 onset to randomization (< 72 hours, \geq 72 hours), SARS-CoV-2 vaccination history, and the total score of the 12 symptoms of COVID-19 at baseline as covariates in participants with mild/moderate SARS-CoV-2 infection whose total score of 12 symptoms of COVID-19 is one or higher at the initiation of administration (Day 1) in the ITT1 population. In addition, as the primary analysis for change from baseline on Day 4 in SARS-CoV-2 viral titer, pairwise comparison will be performed between each S-217622 intervention group and the placebo group, analysis of covariance will be applied with change from baseline on Day 4 in SARS-CoV-2 viral titer as response, and by time from COVID-19 onset to randomization (< 72 hours, \geq 72 hours), SARS-CoV-2 vaccination history, and SARS-CoV-2 viral titer at baseline as covariates in participants with mild/moderate SARS-CoV-2 infection in the ITT1 population. The multiplicity adjustment will be performed in these pairwise comparisons by using a fixed-sequence procedure.

Primary Endpoint in Phase 3 Part (Participants with Mild/Moderate SARS-CoV-2 Infection)

The primary endpoint in Phase 3 Part for participants with mild/moderate SARS-CoV-2 infection, ie, the time to improvement of COVID-19 symptoms is defined as the time from the start of the study intervention to improvement of all 12 symptoms of COVID-19 (low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath [difficulty breathing], nausea, vomiting, and diarrhea). The improvement of symptoms is defined in the footnotes to Objectives and Endpoints.

As the primary analysis for this primary endpoint, a pairwise comparison of the time to improvement of COVID-19 symptoms will be performed between each S-217622 treatment group and the placebo group using a log-rank test stratified by the time from

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COVID-19 onset to randomization (< 72 hours, \geq 72 hours) and SARS-CoV-2 vaccination history at a one-sided significance level of 0.025 in the participants with mild/moderate SARS-CoV-2 infection population of participants who have at least 3 moderate symptoms in the ITT2 population. In addition, in the mild/moderate SARS-CoV-2 infection population of participants who have at least 1 moderate symptom in the ITT2 population, a similar analysis will be performed as a key secondary analysis. The multiplicity adjustment will be applied to the primary analysis. The following analyses will be performed as other analyses.

- Pairwise comparison using the generalized Wilcoxon test stratified by time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history between each S-217622 treatment group and the placebo group will be performed.
- Kaplan-Meier curves will be plotted for each treatment group and the median time to improvement of COVID-19 symptoms and its 95% confidence interval (CI) will be calculated. Moreover, the difference in median between treatment groups and its 95% CI will be calculated.
- The hazard ratio of each S-217622 treatment group to the placebo group will be estimated using a Cox proportional hazard model stratified by time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history.
- Restricted mean survival time (RMST) with a 21-day investigation period will be estimated for each treatment group and pairwise comparison between each S-217622 treatment group and the placebo group will be performed.

<u>Primary Endpoint in Phase 2b/3 Part (Participants with Asymptomatic/Mild</u> <u>Symptoms Only SARS-CoV-2 Infection)</u>

The primary endpoint in Phase 2b/3 Part for participants with asymptomatic/mild symptoms only SARS-CoV-2 infection, ie, the proportion of participants with development/worsening of COVID-19 symptoms, is defined as the proportion of participants in the asymptomatic/mild symptoms only SARS-CoV-2 infection population in the ITT2 population with development/worsening of any of the 12 symptoms of COVID-19, taste disorder, or smell disorder by 14 days after the first administration of the study intervention. The development/worsening of symptoms is determined according to the protocol-specified rules.

As the primary analysis for this primary endpoint, a pairwise comparison of the proportion of participants with development/worsening of COVID-19 symptoms will be performed between each S-217622 treatment group and the placebo group using

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the Mantel-Haenszel test stratified by SARS-CoV-2 vaccination history at a one-sided significance level of 0.025 in the participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in the ITT2 population. The multiplicity adjustment will be applied to the primary analysis.

As an additional analysis for this primary endpoint, the risk ratio of each S-217622 treatment group to the placebo group will be estimated.

Key Secondary Endpoint in Phase 3 Part and Phase 2b/3 Part

The key secondary endpoint in Phase 3 Part and Phase 2b/3 Part, ie, the time to the first negative SARS-CoV-2 viral titer, is defined as the time from the start of the study intervention to the first confirmed drop of SARS-CoV-2 viral titer below the detection limit. Participants whose SARS-CoV-2 viral titer was not confirmed to be negative will be handled as censored cases according to the time of the last evaluation of SARS-CoV-2 virus titer or the time of the last evaluation of SARS-CoV-2 virus titer before the first administration of protocol-specified prohibited concomitant drug, whichever is earlier.

The primary analysis for this key secondary endpoint is planned for participants with mild/moderate SARS-CoV-2 infection and those with asymptomatic/mild symptoms only SARS-CoV-2 infection separately. Pairwise comparison of the time to the first negative SARS-CoV-2 viral titer will be performed between each S-217622 treatment group and the placebo group using a log-rank test stratified by the time from COVID-19 onset to randomization (< 72 hours, \geq 72 hours) and SARS-CoV-2 vaccination history at a one-sided significance level of 0.025 in participants with mild/moderate SARS-CoV-2 infection in mITT population of each Phase 3 Part and Phase 2b/3 Part. Pairwise comparison of the time to the first negative SARS-CoV-2 viral titer will be compared between each S-217622 treatment group and the placebo group using a log-rank test stratified by the SARS-CoV-2 viral titer will be compared between each S-217622 treatment group and the placebo group using a log-rank test stratified by the SARS-CoV-2 vaccination history at a one-sided significance level of 0.025 in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in the mITT population. The multiplicity adjustment will be applied to the primary analysis.

The following analyses will be performed as additional analyses for the key secondary endpoint. The multiplicity adjustment as planned for the primary analysis will not be performed for statistical tests involving between-group comparisons that will be performed in the following analyses.

 Pairwise comparison will be performed using the generalized Wilcoxon test stratified by the time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history between each S-217622

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S-217622 treatment group and the place		
 SARS-CoV-2 infection. Pail generalized Wilcoxon test st between each S-217622 treat participants with asymptomatic participants with asymptomatic/mild symptomatic/mild symptom curves of each group will be SARS-CoV-2 viral titer and difference in median betweet calculated. The hazard ratio of each S-2 be estimated using a Cox pr from COVID-19 onset to rat CoV-2 vaccination history i CoV-2 infection. The hazard placebo group will be estimated by SARS-CoV-2 vacuasymptomatic SARS-CoV-2 v	tratified by the SARS-CoV- atment group and the placeb atic/mild symptoms only SA hoderate SARS-CoV-2 infection in sonly SARS-CoV-2 infection plotted, and the median time is 95% CI will be calculated on treatment groups and its 9 217622 treatment group to the oportional hazard model star ndomization (< 72 hours, \geq n the participants with mild d ratio of each S-217622 treat ated using a Cox proportion vaccination history in the participants in the participants with mild	-2 vaccination history o group in the ARS-CoV-2 infection. action and those with tion, Kaplan-Meier ne to the first negative ed. Moreover, the 95% CI will be he placebo group will atified by the time 72 hours) and SARS- /moderate SARS- atment group to the nal hazard model rticipants with
 For participants with mild/n asymptomatic/mild symptom 21-day investigation period pairwise comparison betwee group will be performed. 	ns only SARS-CoV-2 infec will be estimated for each t	tion, RMST with a reatment group, and a
Safety Analyses:		
All safety analyses were to be perfor Phase 2a Part, Phase 2b Part, Phase combined. In merged Parts, analyse CoV-2 infection population, the asy infection population, and the merge	3 Part, and Phase 2b/3 Part s will be performed in the r mptomatic/mild symptoms	, and these parts nild/moderate SARS- only SARS-CoV-2
AEs were coded and classified by s using the Medical Dictionary for Re number and proportion of participat events (TEAEs), TEAEs with an ou	egulatory Activities (MedD nts who experienced treatm	RA) Version 24.0. The ent-emergent adverse

and TEAE leading to discontinuation of the study intervention were summarized by treatment group. The number and proportion of participants who experienced TEAEs

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in each category of severity and outcome were summarized by SOC and PT for each Part. Treatment-related TEAEs were summarized in the same manner as TEAEs.

For laboratory test values and vital signs, summary statistics of measurement values and their changes from baseline were calculated by treatment group for each scheduled time point. Qualitative laboratory data were summarized by the numbers of participants in the test categories at baseline and scheduled time points using shift tables.

For ECGs (Phase 2a Part only), summary statistics for ECG interpretations (normal, abnormal but not clinically significant, or abnormal and clinically significant) at each scheduled time point after randomization (including baseline) were calculated for each treatment group.

PK Analyses:

For the PK concentration population, plasma S-217622 concentrations were listed for each treatment group and Day along with the time elapsed from the last dosing of study intervention prior to blood sampling each for Phase 2a Part, Phase 2b Part, Phase 3 Part and Phase 2b/3 Part. Plasma trough concentrations (C₂₄) defined as plasma S-217622 concentrations within 20 to 28 hours after the first dose on Day 2 were summarized by treatment group and part with N, mean (Mean), standard deviation (SD), coefficient of variation (CV%, calculated as SD/mean × 100), geometric mean and its coefficient of variation (CV% geometric mean, calculated as $\{\exp [sd^2] - 1\}^{1/2} \times 100$, where sd was the SD of natural log-transformed values), median (Median), minimum (Min), and maximum (Max) each for Phase 2a Part, Phase 2b Part, Phase 3 Part and Phase 2b/3 Part. If possible, C₂₄ were summarized by age group (12 to 18 years old, 19 to 64 years old, and over 65 years old). The data were not to be summarized for a group with N less than 3. The plasma concentrations of S-217622 versus the time from the last dosing of study intervention prior to blood sampling were graphically presented at the linear scale by treatment group.

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Summary of Results:

Efficacy (Phase 2a Part):

Data Sets Analyzed

- A total of 69 participants were randomized to one of the treatment groups.
- For all participants (with mild/moderate and asymptomatic SARS-CoV-2 infection combined), the mITT population consisted of 43 participants (15 in the S-217622 125 mg group, 14 in the S-217622 250 mg group, and 14 in the placebo group) (hereafter in the same order), while the ITT population consisted of 47 participants (16, 14, and 17).
- As for participants with mild/moderate SARS-CoV-2 infection, the mITT population consisted of 37 participants (13, 12, and 12), while the ITT population consisted of 40 participants (14, 12, and 14).
- As for participants with asymptomatic SARS-CoV-2 infection, the mITT population consisted of 6 participants (2, 2, and 2), while the ITT population consisted of 7 participants (2, 2, and 3).

Demographics and Other Baseline Characteristics

- All 69 randomized participants of Phase 2a Part were Japanese.
- As for participants with mild/moderate SARS-CoV-2 infection in the ITT population, the proportion of male participants was greater in the placebo group than in the S-217622 treatment groups; male participants accounted for 42.9% (6/14) in the S-217622 125 mg group, 50.0% (6/12) in the S-217622 250 mg group, and 78.6% (11/14) in the placebo group (hereafter in the same order). The median age (range) was 34.5 years (22–59), 37.5 years (23–63), and 35.0 years (16–61), respectively, being comparable across the treatment groups. No participants under 20 years of age were enrolled in the S-217622 treatment groups. The time from disease onset to enrollment was ≥ 72 hours in the majority of participants in all treatment groups: 64.3% (9/14), 58.3% (7/12), and 64.3% (9/14), respectively. A great majority of participants had received COVID-19 vaccination in all treatment groups: 85.7% (12/14), 83.3% (10/12), and 71.4% (10/14), respectively.
- As for participants with asymptomatic SARS-CoV-2 infection in the ITT population, all participants were male except for one in the placebo group. The age was 41 and 47 years in the S-217622 125 mg group, 37 and 41 years in the S-217622 250 mg group, and 37, 45, and 51 years in the placebo group, being comparable across the treatment groups. No participants under 20 years of age

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were enrolled in any treatment groups. All participants except for one in the placebo group had received COVID-19 vaccination.

Primary Endpoint

For all participants (with mild/moderate and asymptomatic SARS-CoV-2 infection combined) in the mITT population:

- The mean (SD) change from baseline in SAR-CoV-2 viral titer (log₁₀ [TCID₅₀/mL]) was -1.05 (1.17) in the S-217622 125 mg group, -2.03 (1.21) in the S-217622 250 mg group, and -0.86 (0.93) in the placebo group on Day 2 (hereafter in the same order), -2.42 (1.42), -2.81 (1.21), and -1.54 (0.74) on Day 4, and -2.56 (1.35), -2.76 (1.19), and -2.08 (0.91) on Day 6, respectively.
- Compared with the placebo group, the change from baseline in SARS-CoV-2 viral titers showed greater decrease by approximately $1 \log_{10} (\text{TCID}_{50}/\text{mL})$ in the S-217622 250 mg group on Day 2, and by approximately $1 \log_{10} (\text{TCID}_{50}/\text{mL})$ in both the S-217622 125 mg and 250 mg groups on Day 4. The change from baseline in SARS-CoV-2 viral titers on Days 2 and 4 was statistically significant in the S-217622 250 mg group, compared with the placebo group (p = 0.0212 and p = 0.0083 each).
- In the post hoc analysis using ANCOVA model, the least squares (LS) means of the change from baseline in SARS-CoV-2 viral titers showed greater decrease by approximately 1 log₁₀ (TCID₅₀/mL) in the S-217622 250 mg group on Day 2, and by approximately 1 log₁₀ (TCID₅₀/mL) in either of the S-217622 125 mg or 250 mg groups on Day 4, compared with the placebo group. The difference in the LS means of change from baseline in SARS-CoV-2 viral titers on Day 2 was statistically significant in the S-217622 250 mg group, compared with the placebo group (p = 0.0129). The difference in the LS means of change from baseline in SARS-CoV-2 viral titers on Day 4 was statistically significant in either the S-217622 125 mg group or 250 mg group, compared with the placebo group (p = 0.00129). The difference in the LS means of change from baseline in SARS-CoV-2 viral titers on Day 4 was statistically significant in either the S-217622 125 mg group or 250 mg group, compared with the placebo group (p = 0.0018 and p = 0.0004 each).

Secondary Endpoints (Common to Participants with Mild/Moderate and with Asymptomatic SARS-CoV-2 Infection)

• For all participants (with mild/moderate and asymptomatic SARS-CoV-2 infection combined) in the mITT population, the median time to first negative SARS-CoV-2 viral titer (the time to when 50% of participants had a negative SARS-CoV-2 viral titer) was shorter in the S-217622 125 mg and 250 mg

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 groups than in the placebo groups (2 days), respectively. For all participants (with mildinfection combined) in the mildinfection combined) in the mildinfection combined) in the mildinfection combined) in the mildinfection combined (4/15), 14.3% (2/14), and 71.4 (2/14), and 30.8% (4/13) on I participants with a positive SJ S-217622 125 mg and 250 mg onward, excepting the S-2176 For all participants (with mildinfection combined) in the IT RT-PCR result (the time to w was approximately 120 hours S-217622 125 mg or 250 mg participants needed a long tim groups. For all participants (with mildinfection combined) in the IT a positive RT-PCR result on I 125 mg group, 78.6% (11/14) (16/17) in the placebo group (57.1% (8/14), and 75.0% (12/ and 66.7% (10/15) on Day 9, a positive RT-PCR result was and 250 mg groups than in th For all participants (with mildinfection combined) in the IT a positive RT-PCR result was and 250 mg groups than in th For all participants (with mildinfection combined) in the IT a positive RT-PCR result was and 250 mg groups than in th For all participants (with mildinfection combined) in the IT baseline in the amount of SAI Day 2 was -1.109 (0.774) in the S-217622 250 mg group, (hereafter in the same order), (1.228) on Day 4, and -3.114 	d/moderate and asymptom ITT population, the proposi- viral titer on Day 2 was 8 4% (10/14) in the S-21762 group (hereafter in the sam 4% (10/14) on Day 4, and Day 6, respectively. The pri- ARS-CoV-2 viral titer was g groups than in the placel 522 125 mg group on Day d/moderate and asymptom T population, the median then 50% of participants h 6 (5 days) shorter numerical groups than in the placebon to become RT-PCR neg d/moderate and asymptom T population, the proportion Day 4 was 93.3% (14/15) in the S-217622 250 mg (hereafter in the same order 16) on Day 6, and 42.9% respectively. The proportion anumerically smaller in the e placebo group on Days (12) 1000000000000000000000000000000000000	atic SARS-CoV-2 rtion of participants 6.7% (13/15) in the 2 250 mg group, and me order), 26.7% 0.0% (0/15), 14.3% roportion of s smaller in the bo group from Day 4 14. atic SARS-CoV-2 time to first negative ad a negative RT-PCR) ally in either the o group, although some gative in all treatment atic SARS-CoV-2 on of participants with in the S-217622 group, and 94.1% er), 66.7% (10/15), (6/14), 53.8% (7/13), ion of participants with e S-217622 125 mg 6 and 9. atic SARS-CoV-2 D) change from (10 [copies/mL]) on (11 + 10 + 10 + 10 + 10 + 10 + 10 + 10 +

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 were greater in the S-217622 group from Day 2 onward. Th RNA were greater by approxin S-217622 125 mg or 250 mg g 4, and by approximately 1.2 to analysis using ANCOVA mod the amount of SARS-CoV-2 v approximately 1 log₁₀ (copies, groups on Day 4, and by appro 125 mg group and approximat 250 mg group on Day 6 comp For participants with mild/mo population, whose baseline 8- oxygen therapy), there was no in the 8-Point Ordinal Scale ir while there were 2 in the place (hospitalized, with oxygen the participants with asymptomati there was no participant whos limitation of activities) in the 125 mg and 250 mg groups w score was not aggravated to ≥ participants. Secondary Endpoints (Participants with suff there to when COVID-19 participants) was 40.6 hours (f group, 55.2 hours (10.3 to 109 36.7 hours (0.1 to 190.7) in th No differences were observed COVID-19 symptoms betwee the placebo group. The estima 80.9 hours, respectively. Altho COVID-19 symptoms was sin 	the decreases in the amount mately 1.4 \log_{10} (copies/m groups compared with the poplo (copies/mL) on Day 6 del, the LS means of the ch viral RNA showed greater of /mL) in either the S-21762 oximately 0.7 \log_{10} (copies/mL) ared with the placebo ground derate SARS-CoV-2 infec Point Ordinal Scale was < participant whose score was n either the S-217622 125 me bo group. The score was n erapy [< 5 L/min]) in any price SARS-CoV-2 infection e score was aggravated to 3 8-Point Ordinal Scale in bo hile there was only 1 in the 2 (symptomatic, limitation ith Mild/Moderate SARS-CoV-2 infection of first improvement of CO symptoms were improved 95%CI, 12.2 to 76.5) in the 0.2) in the S-217622 250 m e placebo group (hereafter in the median time to first n either of the S-217622 tr the RMST was 57.9 hours ough the median time to first ough the median time to first	of SARS-CoV-2 viral L) in either the placebo group on Day . In the post hoc ange from baseline in decrease by 2 125 mg or 250 mg s/mL) in the S-217622 in the S-217622 up. tion in the ITT 3 (hospitalized, no vas aggravated to \geq 3 mg or 250 mg groups not aggravated to \geq 4 varticipants. For in the ITT population, \geq 1 (symptomatic, no oth the S-217622 e placebo group. The n of activities) in any COV-2 Infection Only) tion in the ITT VID-19 symptoms in 50% of e S-217622 125 mg ng group, and in the same order). timprovement of reatment groups and a, 81.6 hours, and rst improvement of

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 a 21-day investigation perioding group compared with the For participants with mild/m population, the mean (SD) che COVID-19 symptoms 12 hou 125 mg group, -2.6 (3.4) in the placebo group (hereafter in the flacebo group (hereafter in the flacebo group stan in the placebo group stan in the placebo group stan in the placebo group, 27.3% (3/11) in the Seplacebo group (hereafter in the 54.5% (6/11) 24 hours post-dose, 83.72 hours post-dose, 81.8% (9 post-dose, respectively. The COVID-19 symptoms tended 125 mg group than in the placebo group (from the flacebo group). The Seplacebo group (hereafter in the 54.5% (6/11) 24 hours post-dose, 83.72 hours post-dose, 81.8% (9 post-dose, respectively. The flacebo group than in the placebo group by 42 hours (frespectively, although the nubaseline was small. 	placebo group. oderate SARS-CoV-2 infe- hange from baseline in the urs post-dose was -4.4 (4. the S-217622 250 mg grou- he same order), -4.8 (3.8) 1-5.8 (5.6), -4.1 (4.1), an decreases in the total score greater in either the S-217 roup from 12 hours post-d oderate SARS-CoV-2 infe- participants with improve e was 25.0% (3/12) in the -217622 250 mg group, ar he same order), 45.5% (5/ dose, 72.7% (8/11), 54.5% (3.3% (10/12), 63.6% (7/11 0/11), 72.7% (8/11), and 6 proportion of participants d to be numerically greater icebo group from 72 hours oderate SARS-CoV-2 infe- to resolution of fever (the s whose fever had resolved 217622 125 mg and 250 m hearly 2 days) and 64 hour	ection in the ITT total score of 3) in the S-217622 up, and -2.1 (1.6) in the , -4.2 (3.5), and -1.6 d -2.9 (2.1) 48 hours e of COVID-19 7622 125 mg or 250 mg ose onward. ection in the ITT ement of COVID-19 S-217622 125 mg ad 54.5% (6/11) in the 11), 45.5% (5/11), and 6 (6/11), and 63.6%), and 60.0% (6/10) 3.6% (7/11) 96 hours with improvement of r in the S-217622 post-dose onward. ection in the ITT time to reach 50% for 1 to < 37.0°C) was ng groups than in the 's (2.5 days),
 Secondary Endpoint (Participants with the number of participants view too small to discuss any trend 		

• The number of participants with asymptomatic SARS-CoV-2 infection was too small to discuss any trends by dose of the proportion of participants with development of COVID-19.

Safety (Phase 2a Part):

Of the 69 randomized participants, 1 participant did not receive the study intervention and was excluded from the safety analysis population. A total of 68 participants with mild/moderate or asymptomatic SARS-CoV-2 infection (21 in the S-217622 125 mg group, 23 in the S-217622 250 mg group, and 24 in the placebo group) were included in the safety analysis population in Phase 2a Part.

No deaths, serious TEAEs, or TEAEs leading to discontinuation of study intervention were reported during the Phase 2a Part of the study. All TEAEs reported in this Part for participants with mild/moderate or asymptomatic SARS-CoV-2 infection are summarized below.

- The overall incidence of TEAEs in Phase 2a Part for the safety analysis population was 52.4% (11/21) in the S-217622 125 mg group, 69.6% (16/23) in the S-217622 250 mg group, and 37.5% (9/24) in the placebo group.
- The overall incidence of treatment-related TEAEs in Phase 2a Part was 23.8% (5/21) in the S-217622 125 mg group, 43.5% (10/23) in the S-217622 250 mg group, and 0% (0/24) in the placebo group.
- The incidences of TEAEs and treatment-related TEAEs were greater in either of the S-217622 treatment groups than in the placebo group, and were smaller in the S-217622 125 mg group than in the S-217622 250 mg groups.
- TEAEs reported in at least 3 participants in any of the treatment groups of Phase 2a Part were high density lipoprotein decreased (14.3% [3/21] and 52.2% [12/23] in the S-217622 125 mg and 250 mg groups, respectively), headache and blood triglycerides increased (13.0% [3/23] each in S-217622 250 mg group). No TEAEs were reported in 3 or more participants in the placebo group. The only treatment-related TEAE reported in at least 3 participants in any of the treatment groups was high density lipoprotein decreased (14.3% [3/21] and 34.8% [8/23] in the S-217622 125 mg and 250 mg groups, respectively).
- No severe TEAEs were reported, and most of TEAEs were categorized as mild. The moderate TEAEs were nasopharyngitis (1 participant in the S-217622 125 mg group), headache and vomiting (one and the same participant in the S-217622 250 mg group). All these moderate events were considered unrelated to the study intervention.
- Most of the TEAEs were resolved or resolving at the last observation. The TEAEs that were not resolved were urine ketone body present (1 participant in the S-217622 125 mg group), hyperbilirubinaemia (1 participant in the S-217622 250 mg group), gamma-glutamyltransferase increased, alanine aminotransferase increased, blood uric acid increased, and protein urine present (1 participant each in the placebo group). All of these events were mild and non-serious, and considered unrelated to the study intervention excluding hyperbilirubinaemia. One TEAE (presyncope) reported in the placebo group and considered unrelated to the study intervention was resolved with sequelae.
- No TEAEs occurred on the loading dose day, and most of the TEAEs occurred on Day 2-7. TEAEs observed from Day 15 onwards were nasopharyngitis (2

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participants), insomnia, fatigue, pyrexia, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased (1 participant each) in the S-217622 125 mg group, and headache (2 participants), nausea, and diarrhoea (1 participant each) in the S-217622 250 mg group, all of which were considered unrelated to S-217622.

CONCLUSIONS

Efficacy Conclusions (Phase 2a Part):

The oral administration of S-217622 once-daily for 5 days (375 mg or 750 mg on Day 1, 125 mg or 250 mg on Days 2 through 5) demonstrated an antiviral effect in participants with mild/moderate or asymptomatic SARS-CoV-2 infection, and was suggested to be clinically effective in patients with mild/moderate SARS-CoV-2 infection, based on the data of 69 participants in Phase 2a Part (40 participants in the ITT population and 37 participants in the mITT population for participants with mild/moderate SARS-CoV-2 infection, 7 participants and 6 participants for participants with asymptomatic SARS-CoV-2 infection, respectively).

Safety Conclusions (Phase 2a Part):

Overall, S-217622 was safe and well tolerated with oral administration of once-daily for 5 days (375 mg or 750 mg on Day 1 and 125 mg or 250 mg on Days 2 through 5) based on the data of 68 participants in Phase 2a Part.

Date of Report: 10 Mar 2022