

# Results from Ph1 and Ph2a studies of S-217622, a novel 3C-like protease inhibitor as once daily oral treatment for SARS-CoV-2 infection

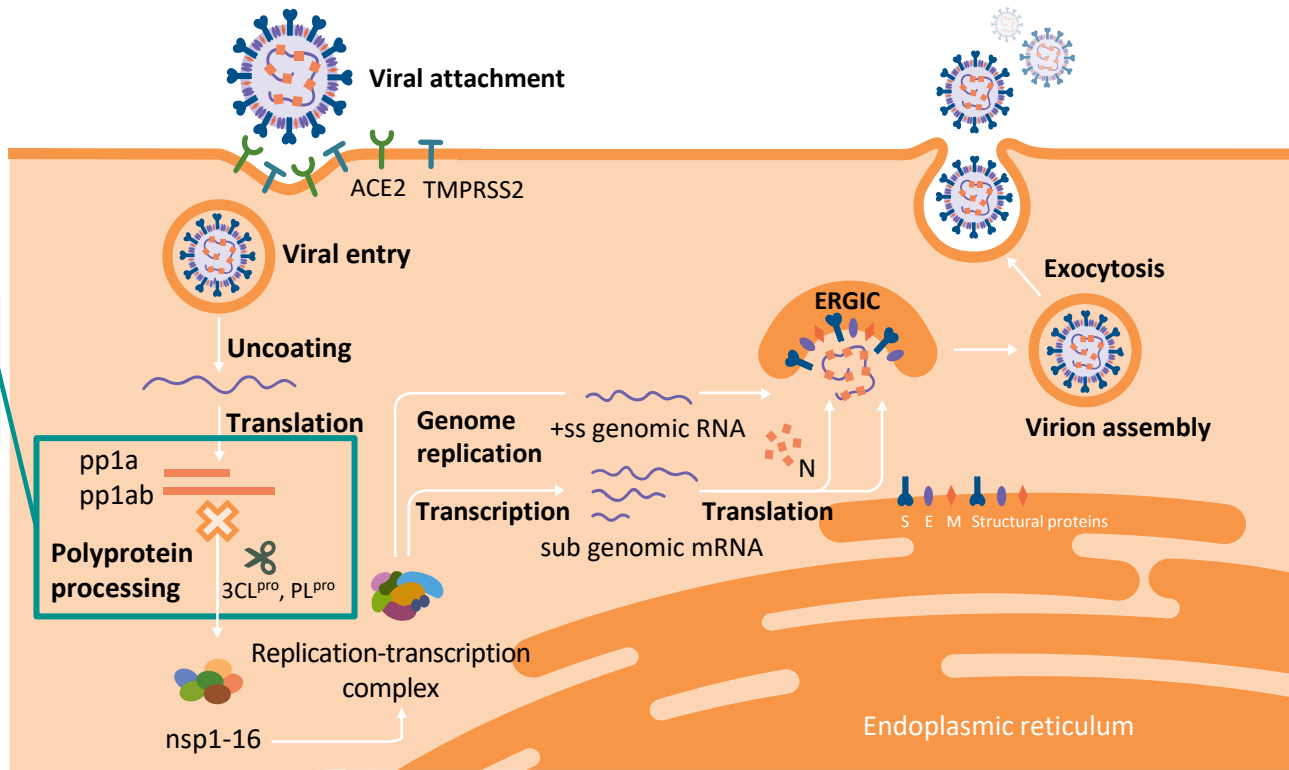
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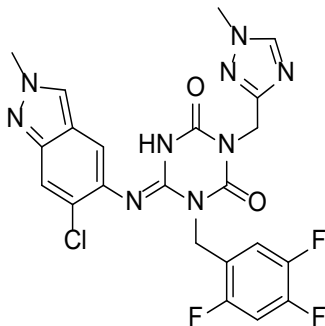
# Transparency declaration

- I have received consulting fees, honoraria for lectures and chairs in sponsored symposiums, supports for attending meetings and travel from Shionogi & Co., Ltd.
- I have received honoraria for lectures and chairs in sponsored symposiums, Support for attending meetings and travel from ViiV Healthcare
- I am a member of S-217622 Advisory Board.
- President of the Japanese Society of Infectious Diseases

# 3CL<sup>pro</sup> is a key enzyme in the viral replication



**3CL<sup>pro</sup> inhibitor  
S-217622**

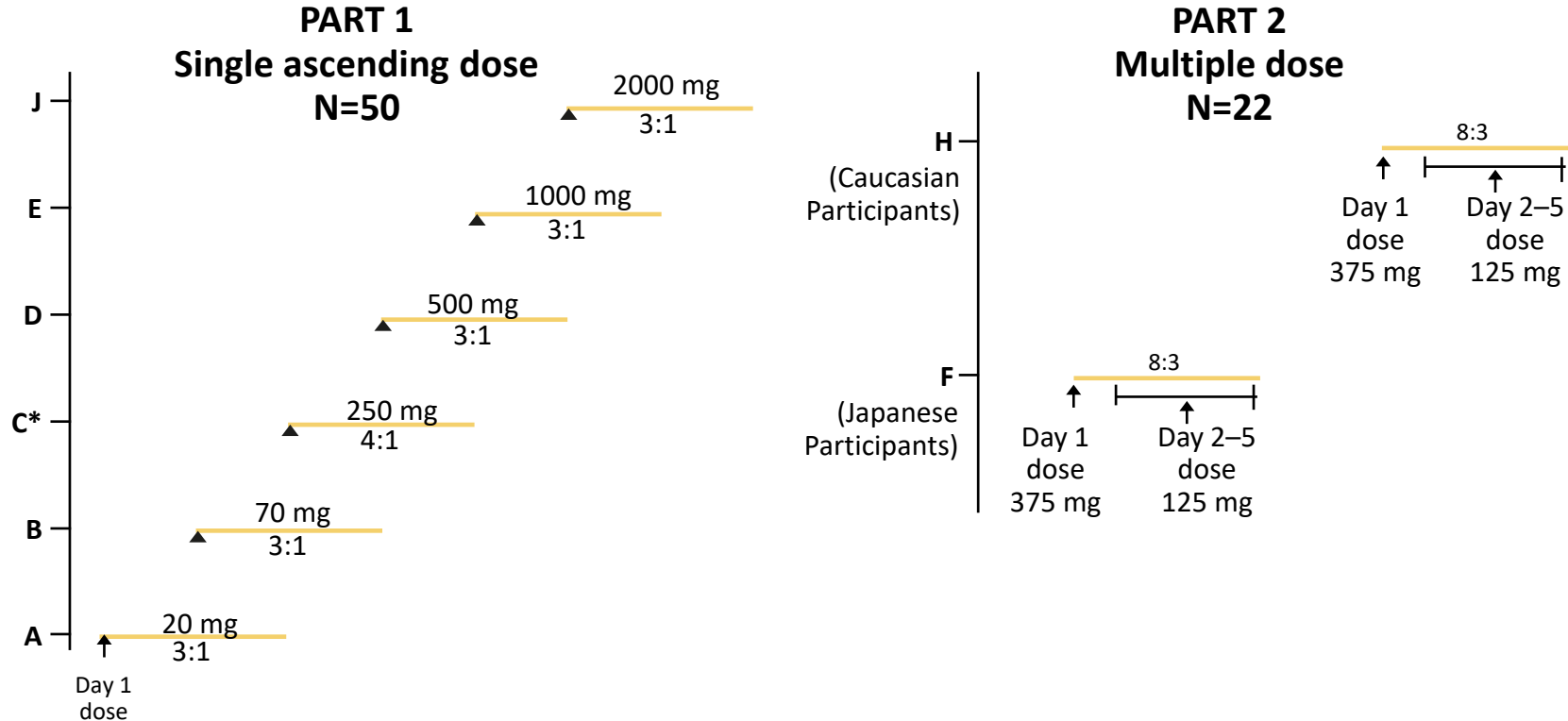


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3CL<sup>pro</sup>, 3C-like protease; ACE2, angiotensin-converting enzyme 2; E, envelope; ERGIC, endoplasmic-reticulum-Golgi intermediate compartment; M, membrane; mRNA, messenger RNA; N, nucleocapsid; nsp1-16, non-structural proteins 1-16; PL<sup>pro</sup>, papain-like protease; pp1a/1ab, polyprotein 1a/1ab; RdRp, RNA-dependent RNA polymerase; RNA, ribonucleic acid; S, spike; ss, single-stranded; TMPRSS2, transmembrane protease serine 2

# Phase 1 study outline

Multicenter, double-blinded, randomized, placebo-controlled study (jRCT2031210202)



\*In Part 1, Cohort C also involved the evaluation of the effect of food on the pharmacokinetics of S-217622

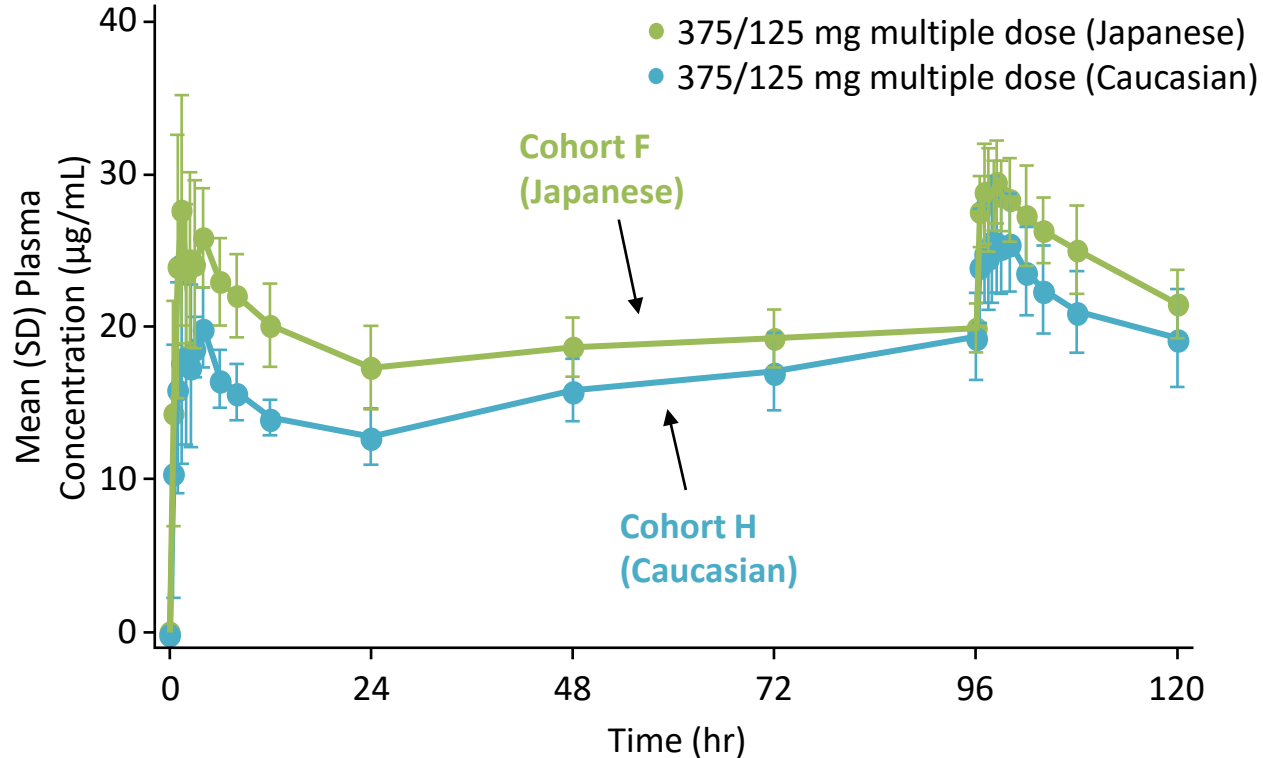
# PK profiles

## PK profile in Part 1 (fasted state)

Parameter	Geometric mean (%CV)					
	20 mg	70 mg	250 mg	500 mg	1000 mg	2000 mg
N	6	6	8	6	6	6
C <sub>max</sub> (µg/mL)	1.70 (15.0)	5.20 (18.5)	15.2 (23.6)	32.6 (19.0)	63.8 (39.1)	96.9 (16.5)
T <sub>max</sub> (hr)	2.50 (1.00, 4.00)	1.50 (1.00, 4.00)	2.50 (1.00, 12.00)	2.00 (1.00, 4.00)	2.75 (1.00, 6.00)	4.00 (1.50, 8.00)
AUC <sub>0-inf</sub> (µg·hr/mL)	91.44 (24.3)	291.0 (15.7)	913.7 (16.2)	1987 (16.1)	3370 (35.5)	6346 (22.2)
t <sub>1/2,z</sub> (hr)	42.6 (18.6)	45.7 (11.9)	43.1 (20.2)	42.2 (14.6)	48.1 (11.3)	43.1 (15.6)

AUC, area under the plasma concentration time curve; AUC<sub>0-inf</sub>, AUC to infinity; C<sub>max</sub>, maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetics; t<sub>1/2,z</sub>, elimination half life; T<sub>max</sub>, time to maximum plasma concentration

# PK profile in Part 2: Japanese vs Caucasian participants



# Safety Ph1

Part 1	S-217622												Placebo	
	Cohort A 20 mg		Cohort B 70 mg		Cohort C fasted 250 mg		Cohort D 500 mg		Cohort E 1000 mg		Cohort J 2000 mg		(fasted state) <sup>b</sup>	
	n=6		n=6		n=8		n=6		n=6		n=6		n=12	
	n (%)	events	n (%)	events	n (%)	events	n (%)	events	n (%)	events	n (%)	events	n (%)	events
Participants with any TEAE	0	0	2 (33.3)	2	0	0	0	0	6 (100)	6	6 (100)	11	0	0
Headache	0	0	1 (16.7)	1	0	0	0	0	0	0	1 (16.7)	1	0	0
Abdominal pain	0	0	1 (16.7)	1	0	0	0	0	0	0	0	0	0	0
Nausea	0	0	0	0	0	0	0	0	0	0	1 (16.7)	1	0	0
Vomiting	0	0	0	0	0	0	0	0	0	0	1 (16.7)	1	0	0
Feces soft	0	0	0	0	0	0	0	0	0	0	1 (16.7)	1	0	0
Chills	0	0	0	0	0	0	0	0	0	0	1 (16.7)	1	0	0
HDL-C decreased	0	0	0	0	0	0	0	0	6 (100)	6	6 (100)	6	0	0

Part 2	S-217622				Placebo			
	Cohort F 125 mg		Cohort H 125 mg		Cohort F 125 mg		Cohort H 125 mg	
	n=8		n=8		n=3		n=3	
	n (%)	events	n (%)	events	n (%)	events	n (%)	events
Participants with any TEAE	7 (87.5)	12	8 (100)	19	0	0	1 (33.3)	1
Headache	0	0	2 (25.0)	4	0	0	0	0
Oropharyngeal pain	0	0	1 (12.5)	1	0	0	0	0
Diarrhea	4 (50)	5	4 (50.0)	6	0	0	1 (33.3)	1
Abdominal pain	0	0	1 (12.5)	1	0	0	0	0
HDL-C decreased	7 (87.5)	7	7 (87.5)	7	0	0	0	0

TEAE, treatment-emergent adverse event HDL-C, High-density lipoprotein Cholesterol

# Phase 2a study outline

<b>Study design</b>	Multicenter, randomized, placebo-controlled, double-blinded study
<b>Study population</b>	Patients with mild/moderate or asymptomatic SARS-CoV-2 infection
<b>Age</b>	12 to <70 years
<b>Endpoints</b>	Virologic response, clinical symptoms, safety
<b>N</b>	69
<b>Dosage and administration</b>	Oral administration of placebo tablet q.d. for 5 days, loading dose at Day 1 followed by 4-day maintenance doses
<b>Intervention groups</b>	S-217622 375/125 mg, S-217622 750/250 mg, or placebo

## Common criteria

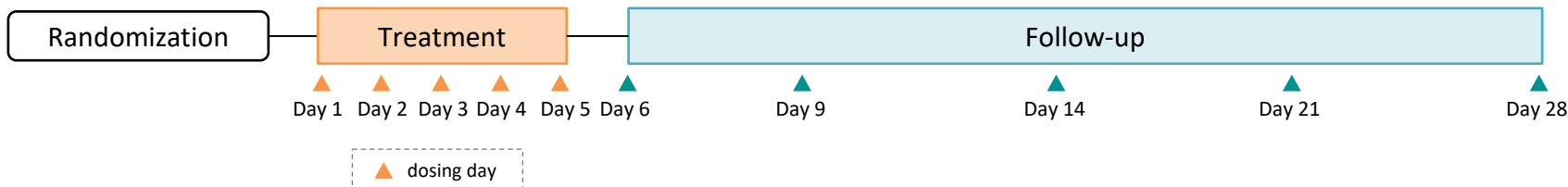
- Aged 12 to 70 years, at the time of signing the informed consent/assent
- Diagnosed as SARS-CoV-2 positive within 120 hours before randomization

## Patients with mild/moderate SARS-CoV-2 infection

- Time from COVID-19 onset to randomization  $\leq 120$  hours
- At least one moderate (COVID-19 score: 2) symptom at enrollment (excluding symptoms present prior to COVID-19 onset)

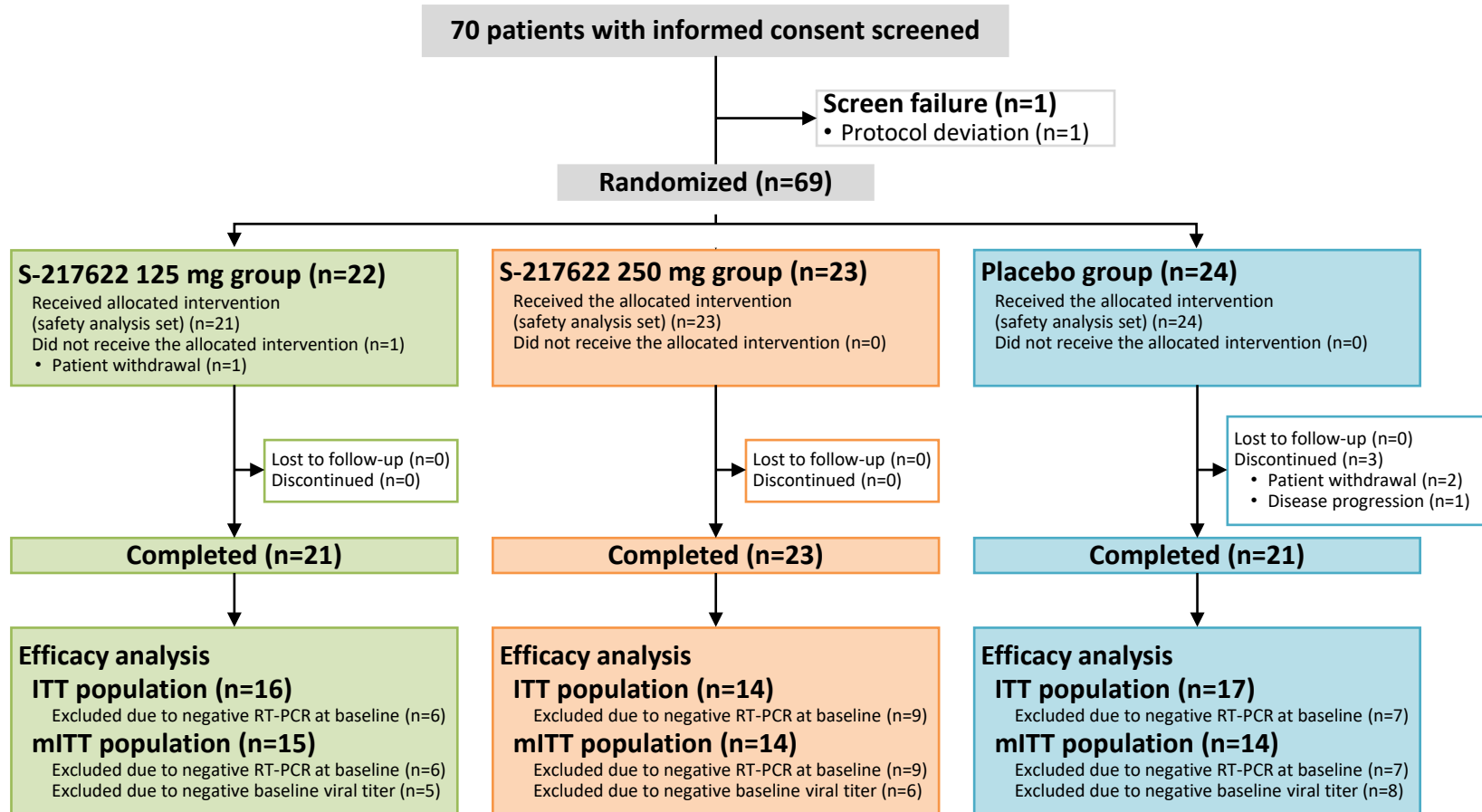
## Patients with asymptomatic SARS-CoV-2 infection

- Patients who have none of the symptoms of COVID-19 within 2 weeks before randomization, or mild symptoms only SARS-CoV-2 infection





# Patient disposition



ITT, intent-to-treat; mITT, modified intent-to-treat; RT-PCR, reverse transcription polymerase chain reaction

# Patient demographics and baseline characteristics (ITT)

		S-217622 125 mg (n=16)	S-217622 250 mg (n=14)	Placebo (n=17)
<b>Sex</b>	Male, %	50.0	57.1	76.5
<b>Age</b>	Years, mean (SD)	38.8 (12.5)	40.4 (10.7)	38.0 (14.2)
<b>Symptom severity</b>	Asymptomatic	2 (12.5)	2 (14.3)	3 (17.6)
	Mild/moderate	14 (87.5)	12 (85.7)	14 (82.4)
<b>Time from onset to randomization (patients with mild/moderate symptoms)</b>	<24 hours	0	0	0
	≥24 to <48 hours	1 (6.3)	0	2 (11.8)
	≥48 to <72 hours	4 (25.0)	5 (35.7)	3 (17.6)
	≥72 to <96 hours	4 (25.0)	4 (28.6)	3 (17.6)
	≥96 to ≤120 hours	5 (31.3)	3 (21.4)	6 (35.3)
	>120 hours	0	0	0
<b>SARS-CoV-2 vaccination status</b>	Yes, %	14 (87.5)	12 (85.7)	12 (70.6)
<b>Virus subtype</b>	Delta	13 (81.3)	13 (92.9)	16 (94.1)
	Omicron	3 (18.8)	1 (7.1)	1 (5.9)

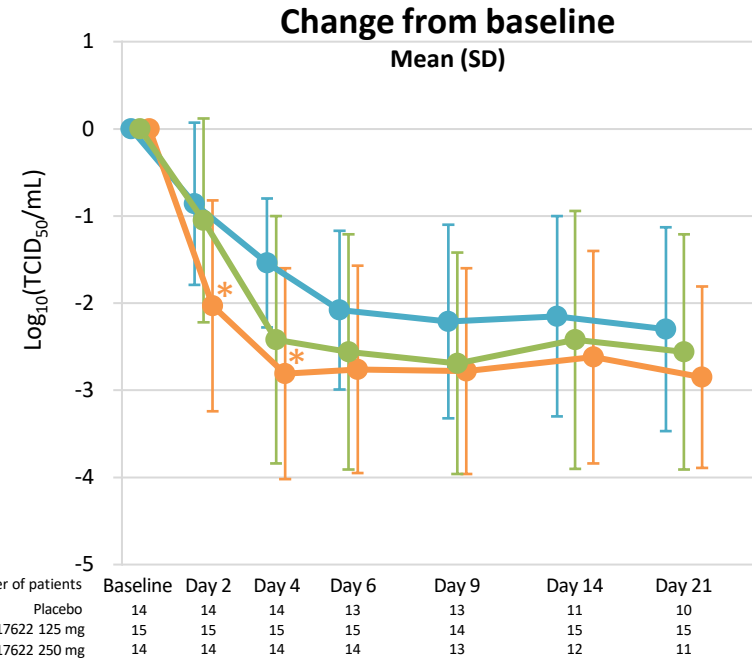
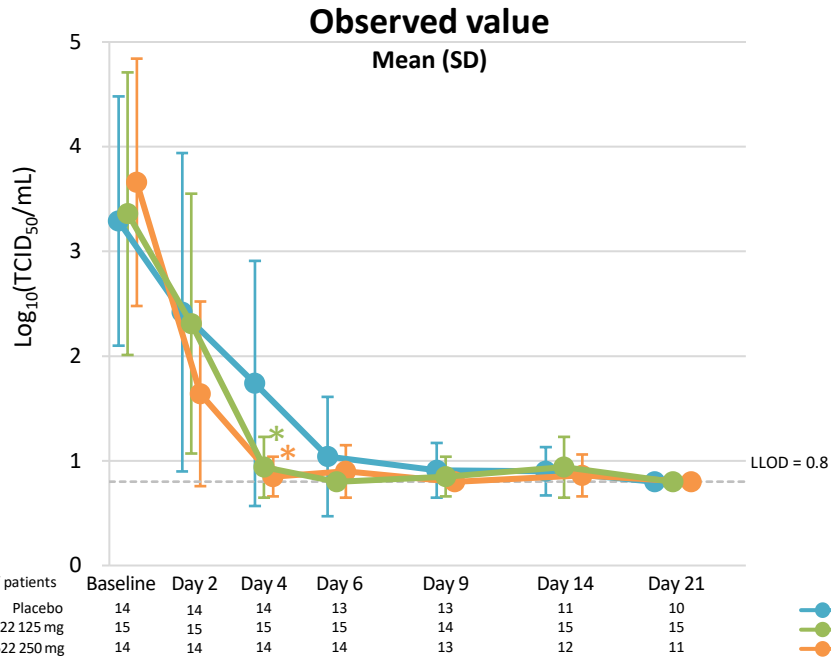
Patients in the S-217622 125 mg group received S-217622 375 mg q.d. on Day 1 followed by 125 mg q.d. on Days 2 to 5.

Patients in the S-217622 250 mg group received S-217622 750 mg q.d. on Day 1 followed by 250 mg q.d. on Days 2 to 5.

Data are n (%), unless stated otherwise. ITT: All patients who were randomly assigned to the study intervention and had a SARS-CoV-2 infection based on RT-PCR.

ITT, intent-to-treat; q.d., once daily; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription polymerase chain reaction; SD, standard deviation

# Primary endpoint: change from baseline in viral titer (mITT)



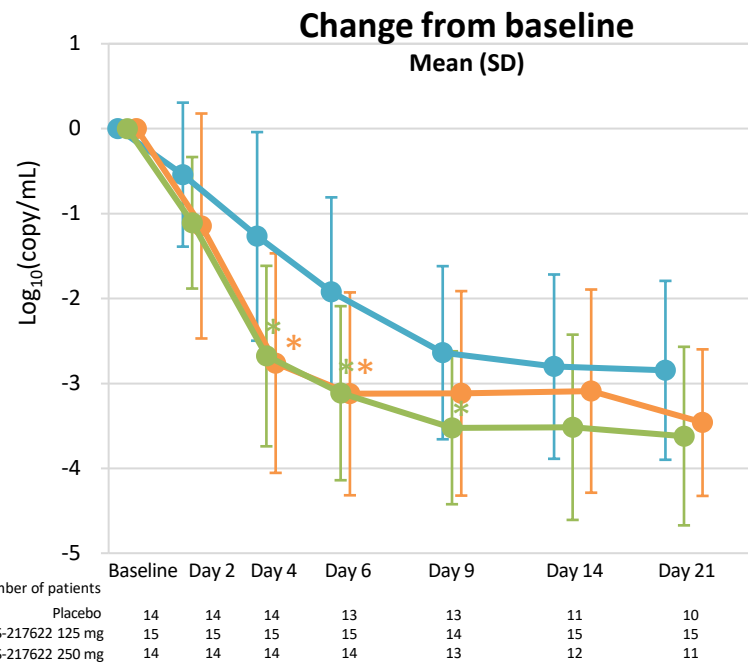
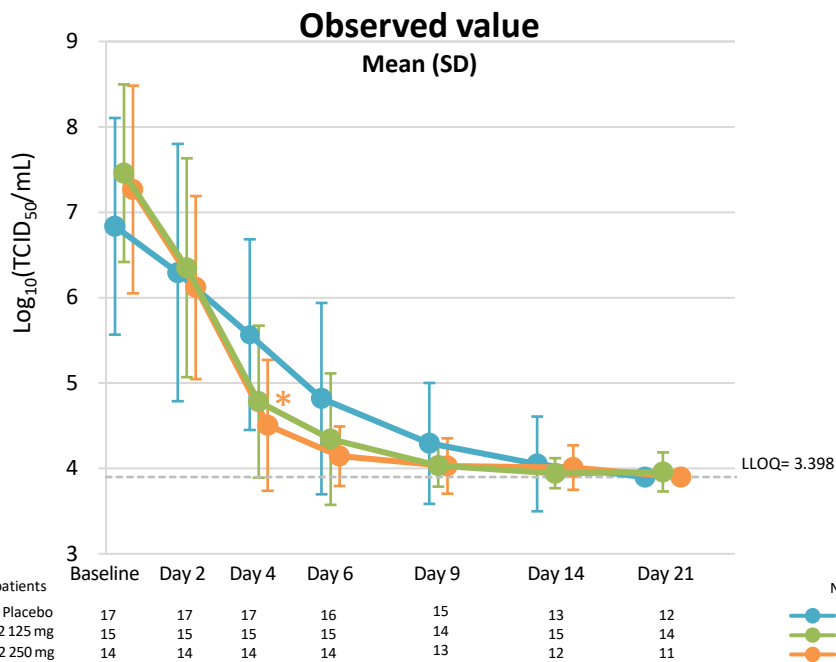
Patients in the S-217622 125 mg group received S-217622 375 mg q.d. on Day 1 followed by 125 mg q.d. on Days 2 to 5.

Patients in the S-217622 250 mg group received S-217622 750 mg q.d. on Day 1 followed by 250 mg q.d. on Days 2 to 5.

mITT population: Patients with positive baseline viral titer. \*p<0.05 vs placebo, van Elteren test stratified by symptom severity cohort (mild/moderate or asymptomatic).

LLOD, lower limit of detection; mITT, modified intent-to-treat; q.d., once daily; SD, standard deviation; TCID<sub>50</sub>, 50% tissue culture infectious dose

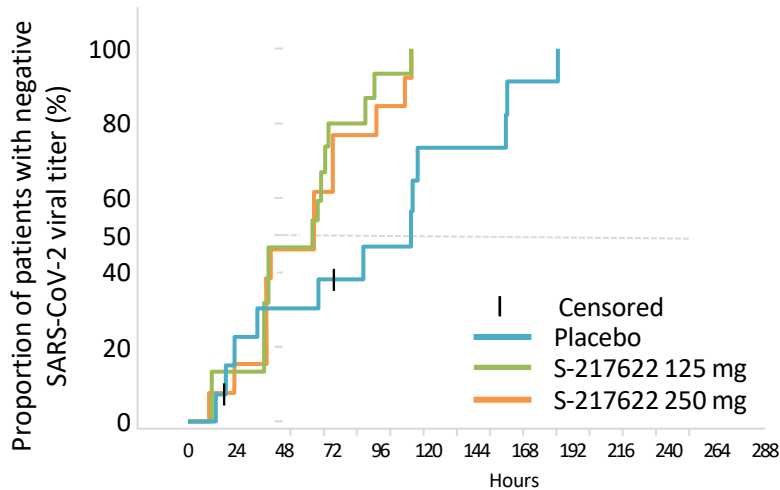
# Secondary endpoint: change from baseline in viral RNA (ITT)



Patients in the S-217622 125 mg group received S-217622 375 mg q.d. on Day 1 followed by 125 mg q.d. on Days 2 to 5.  
 Patients in the S-217622 250 mg group received S-217622 750 mg q.d. on Day 1 followed by 250 mg q.d. on Days 2 to 5.

ITT: All patients randomly assigned to the study intervention and had a SARS-CoV-2 infection based on RT-PCR. \*p<0.05 vs placebo, van Elteren test stratified by symptom severity cohort (mild/moderate or asymptomatic).  
 LLOQ, lower limit of quantification; ITT, intent-to-treat; q.d., once daily; SD, standard deviation

# Secondary endpoint: time to the first negative viral titer (mITT)



	0	24	48	72	96	120	144	168	192	216	240	264	288
Placebo	14	10	9	8	6	3	3	1	0	0	0	0	0
S-217622 125 mg	15	13	8	3	1	0	0	0	0	0	0	0	0
S-217622 250 mg	13	11	7	5	2	0	0	0	0	0	0	0	0

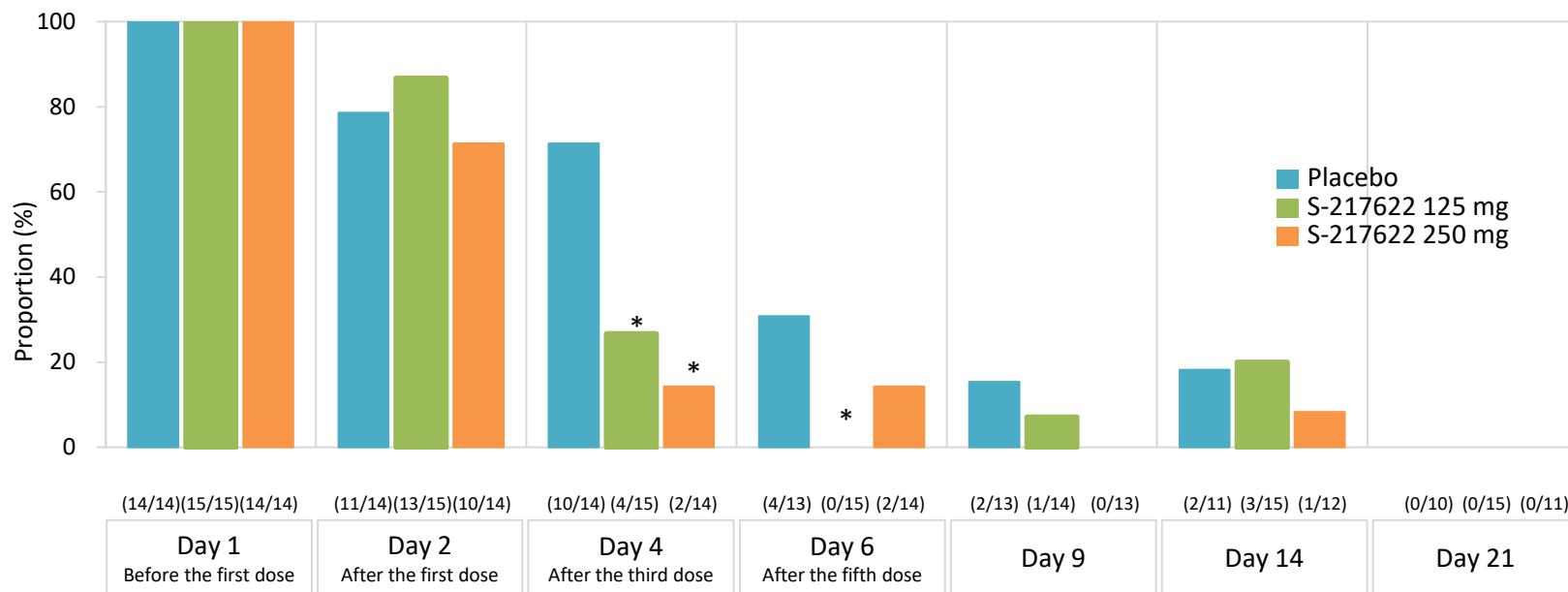
	S-217622 125 mg (n=15)	S-217622 250 mg (n=13)	Placebo (n=14)
<b>Time to negative viral SARS-CoV-2 titer, hours</b>	61.3 (38.0, 68.4)	62.7 (39.2, 72.3)	111.1 (23.2, 158.5)
<b>Difference vs. placebo</b>	-49.8 (-96.7, 30.9)	-48.4 (-95.9, 28.5)	—
<b>P-value<sup>a</sup></b>	0.0159	0.0205	—

Data are median (95% CI).

<sup>a</sup>Log-rank test stratified by symptom severity cohort (mild/moderate or asymptomatic/only mild symptoms).

Patients in the S-217622 125 mg group received S-217622 375 mg q.d. on Day 1 followed by 125 mg q.d. on Days 2 to 5.  
 Patients in the S-217622 250 mg group received S-217622 750 mg q.d. on Day 1 followed by 250 mg q.d. on Days 2 to 5.  
 One patient in the S-217622 250 mg was excluded owing to use of a prohibited concomitant drug on Day 1.  
 CI, confidence interval; mITT, modified intent-to-treat; q.d., once daily; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

# Secondary endpoint: proportion of patients with a positive viral titer (mITT)



Patients in the S-217622 125 mg group received S-217622 375 mg q.d. on Day 1 followed by 125 mg q.d. on Days 2 to 5.

Patients in the S-217622 250 mg group received S-217622 750 mg q.d. on Day 1 followed by 250 mg q.d. on Days 2 to 5.

mITT population: Patients with positive baseline viral titer. <sup>a</sup>>0.8 log<sub>10</sub>(TCID<sub>50</sub>/mL). \*p<0.05 vs placebo, Mantel-Haenszel test stratified by symptom severity cohort (mild/moderate or asymptomatic).

mITT, modified intent-to-treat; q.d., once daily; TCID<sub>50</sub>, 50% tissue culture infectious dose

# Safety Ph2a

	S-217622 125 mg (n=21) n (%)	S-217622 250 mg (n=23) n (%)	Placebo (n=24) n (%)
<b>Number of participants with any TEAE</b>	11 (52.4)	16 (69.6)	9 (37.5)
<b>TEAE leading to discontinuation of study intervention</b>	0	0	0
<b>TEAE reported in ≥5% of patients in any group</b>			
Nasopharyngitis	2 (9.5)	0	0
Headache	1 (4.8)	3 (13.0)	0
Rhinalgia	2 (9.5)	0	0
HDL Cholesterol decreased	3 (14.3)	12 (52.2)	2 (8.3)
TG increased	0	3 (13.0)	0
AST increased	1 (4.8)	1 (4.3)	2 (8.3)
Blood bilirubin increased	0	2 (8.7)	0
ALT increased	1 (4.8)	0	2 (8.3)
<b>Subjects with any Treatment-related TEAE</b>	5 (23.8)	10 (43.5)	0
<b>Treatment-related TEAE reported in ≥5% of patients in any group</b>			
HDL Cholesterol decreased	3 (14.3)	8 (34.8)	0
TG increased	0	2 (8.7)	0
<b>Serious adverse event</b>	0	0	0

AST, aspartate aminotransferase; HDL, high density lipoprotein; TG, triglyceride; TEAE, treatment-emergent adverse event

# Conclusions

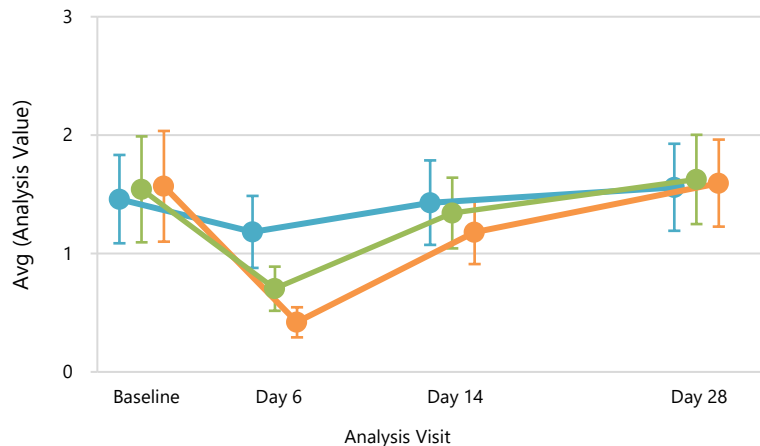
- Data presented in Ph1 first-in-human study indicate that S-217622 was well tolerated in healthy individuals, and the pharmacokinetics evaluations highlighted the potential for once-daily administration
- In Ph2a, treatment with 5-day oral administration of S-217622 demonstrated a rapid clearance of SARS-CoV-2 and was well tolerated in patients with mild-to-moderate or asymptomatic infection
- The results support further clinical development of S-217622 through large-scale clinical studies for the treatment of mild-to-moderate or asymptomatic SARS-CoV-2 infection



# Appendix

# HDL Cholesterol, Triglycerides in Ph2a

## HDL Cholesterol (mmol/L)



## Triglycerides (mmol/L)

