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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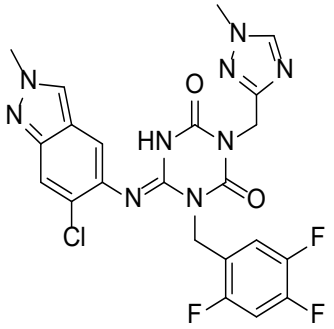
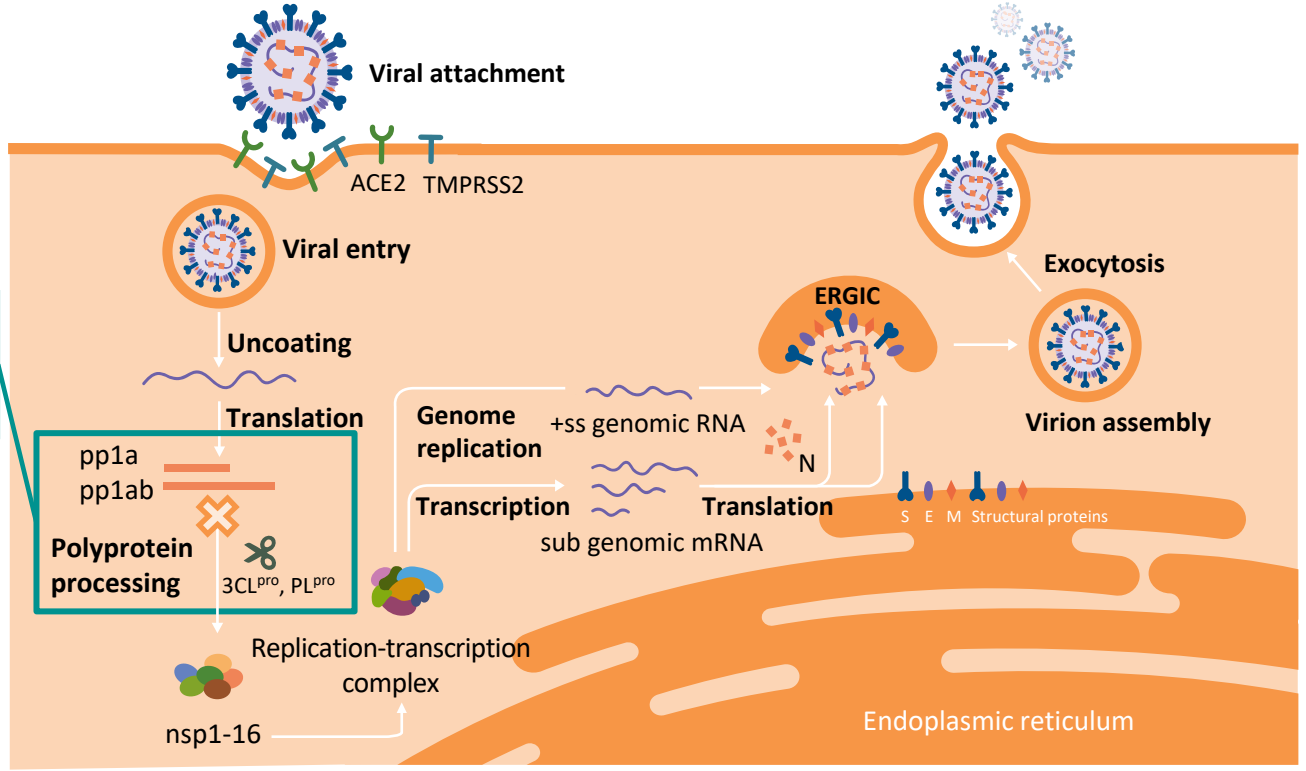
Transparency declaration

- 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^{pro} is a key enzyme in the viral replication

3CL^{pro} inhibitor S-217622





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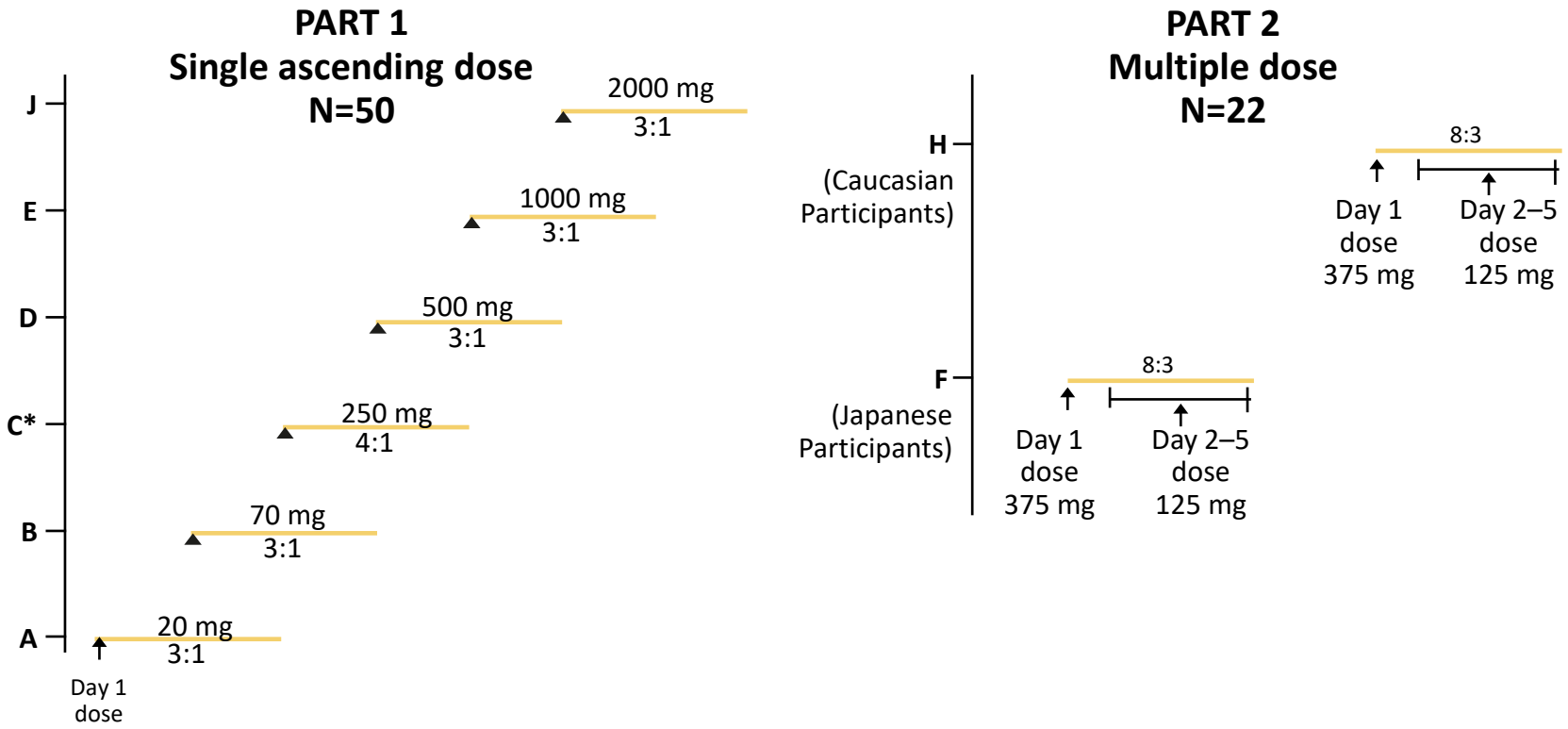
3CL^{pro}, 3C-like protease; ACE2, angiotensin-converting enzyme 2; E, envelope; ERGIC, endoplasmic-reticulum-Golgi intermediate compartment; M, membrane; mRNA, messenger RNA; N, nucleocapsid; nsp1-16, non-structural proteins 1-16; PL^{pro}, papain-like protease; pp1a/1ab, polyprotein 1a/1ab; RdRp, RNA-dependent 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

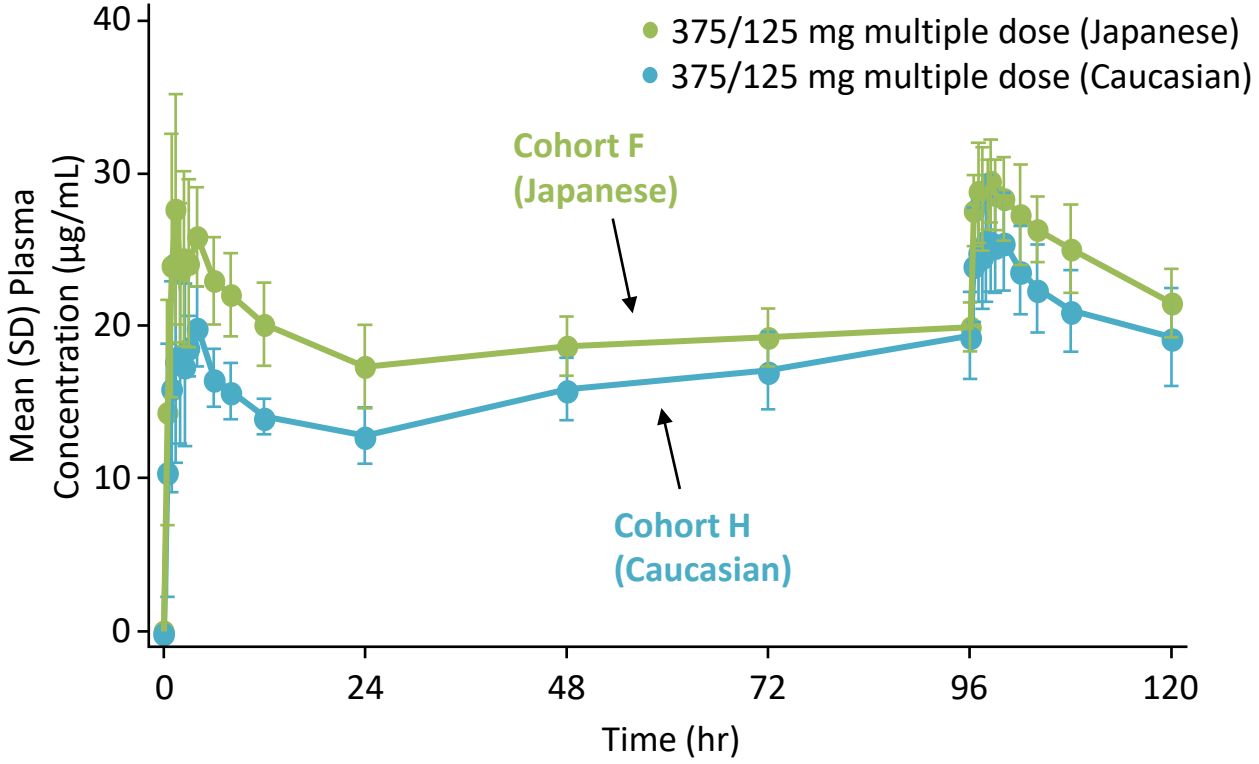
PK profiles

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_{max} (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_{max} (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)
$AUC_{0\text{-}inf}$ (µg·hr/mL)	91.44 (24.3)	291.0 (15.7)	913.7 (16.2)	1987 (16.1)	3370 (35.5)	6346 (22.2)
$t_{1/2,z}$ (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_{0-inf}, AUC to infinity; C_{max}, maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetics; $t_{1/2,z}$, elimination half life; T_{max}, 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)[b]	
	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

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

Common criteria

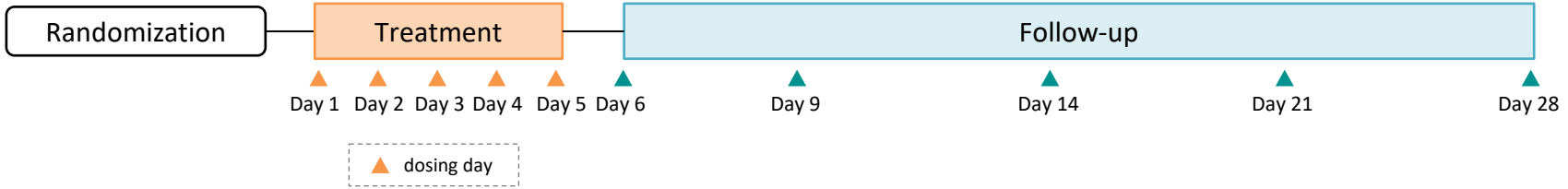
- Aged 12 to 70 years, at the time of signing the informed consent/assent
- Diagnosed as SARS-CoV-2 positive within 120 hours before randomization

Patients with mild/moderate SARS-CoV-2 infection

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

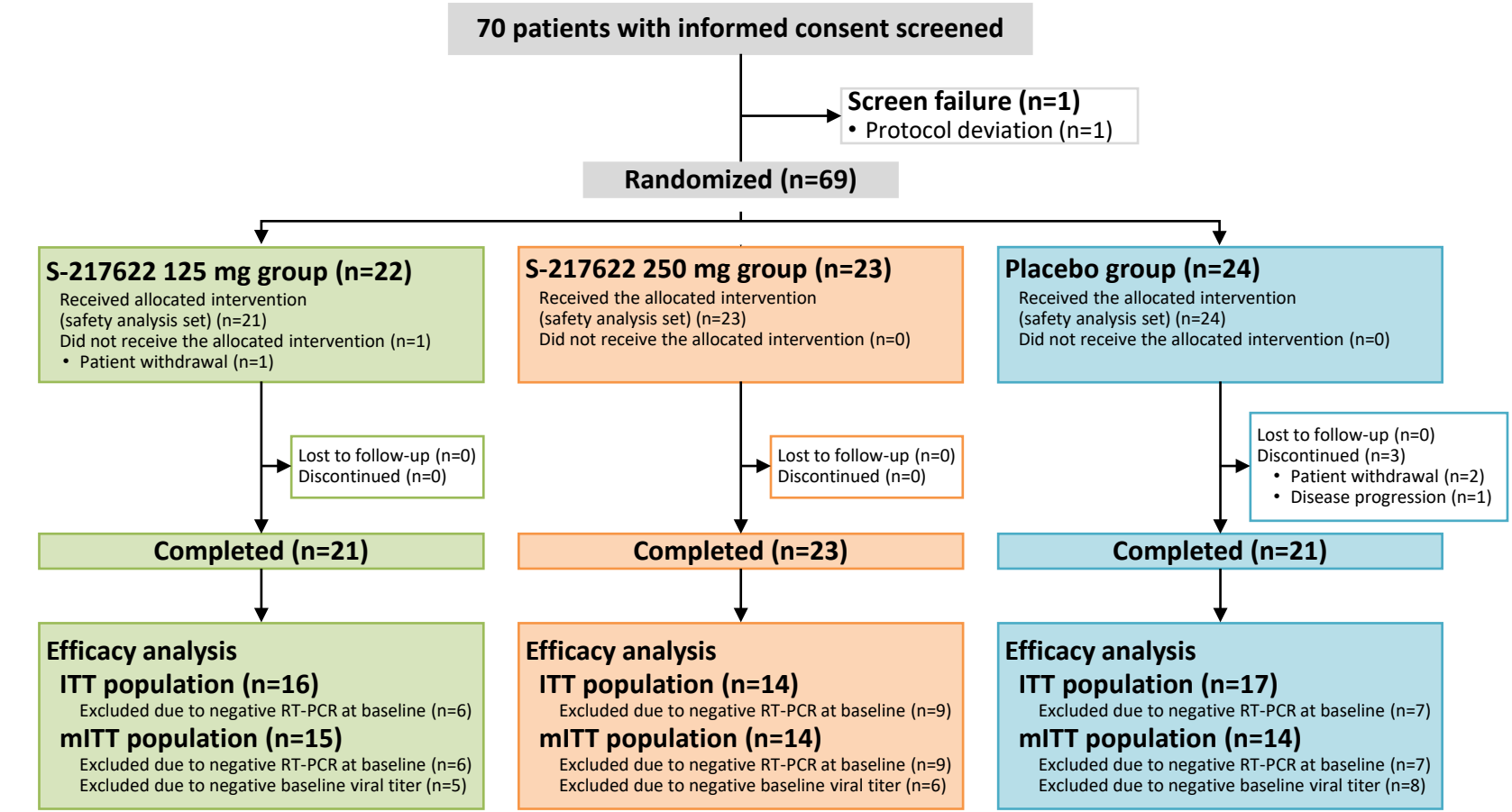
Patients with asymptomatic SARS-CoV-2 infection

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



COVID-19, coronavirus disease 2019; q.d., once daily; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Patient disposition



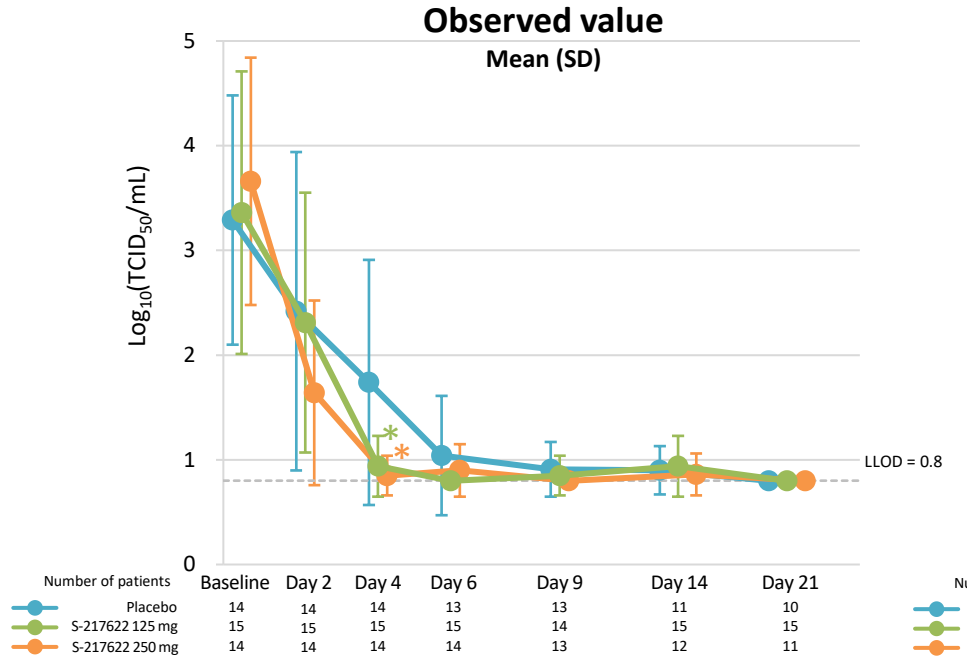
ITT, intent-to-treat; mITT, modified intent-to-treat; RT-PCR, reverse transcription polymerase chain reaction

Patient demographics and baseline characteristics (ITT)

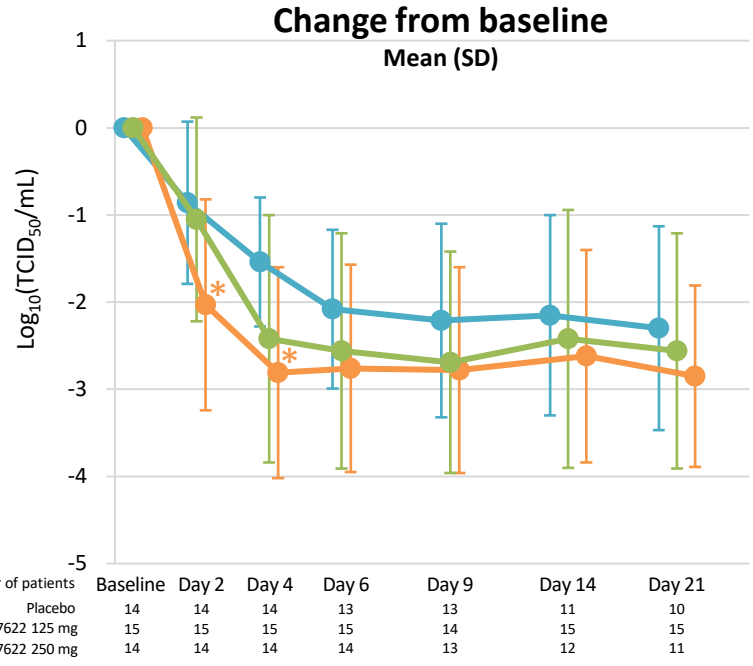
		S-217622 125 mg (n=16)	S-217622 250 mg (n=14)	Placebo (n=17)
Sex	Male, %	50.0	57.1	76.5
Age	Years, mean (SD)	38.8 (12.5)	40.4 (10.7)	38.0 (14.2)
Symptom severity	Asymptomatic	2 (12.5)	2 (14.3)	3 (17.6)
	Mild/moderate	14 (87.5)	12 (85.7)	14 (82.4)
Time from onset to randomization (patients with mild/moderate symptoms)	<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
SARS-CoV-2 vaccination status	Yes, %	14 (87.5)	12 (85.7)	12 (70.6)
Virus subtype	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)



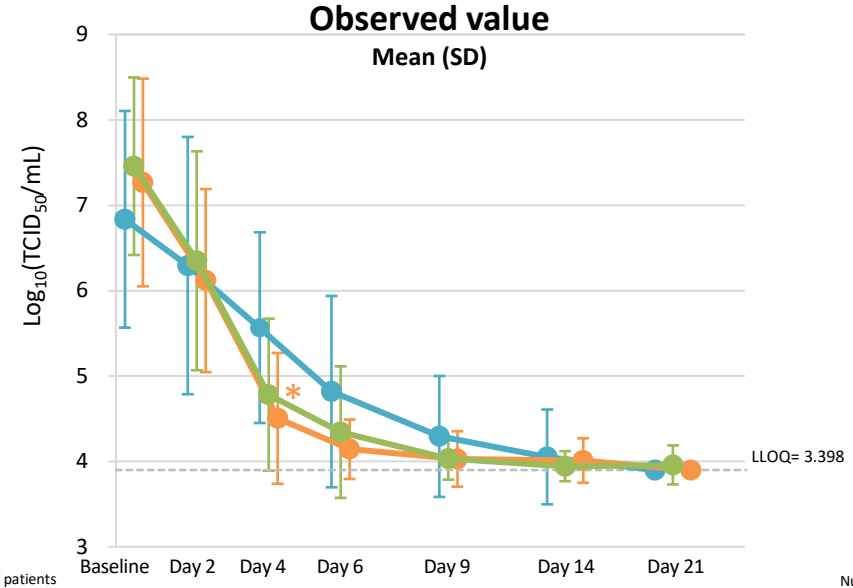
Number of patients	Baseline	Day 2	Day 4	Day 6	Day 9	Day 14	Day 21
Placebo	14	14	14	13	13	11	10
S-217622 125 mg	15	15	15	15	14	15	15
S-217622 250 mg	14	14	14	14	13	12	11

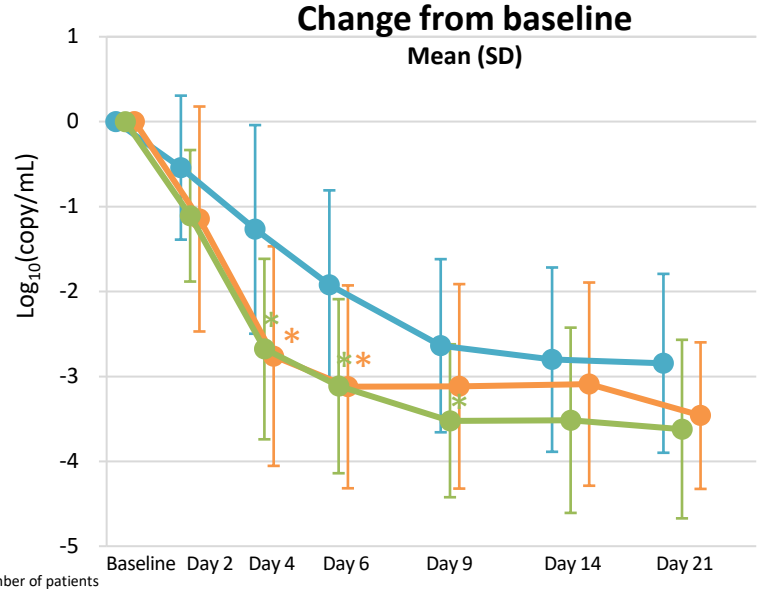


Number of patients	Baseline	Day 2	Day 4	Day 6	Day 9	Day 14	Day 21
Placebo	14	14	14	13	13	11	10
S-217622 125 mg	15	15	15	15	14	15	15
S-217622 250 mg	14	14	14	14	13	12	11

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; $TCID_{50}$, 50% tissue culture infectious dose

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





Number of patients	Baseline	Day 2	Day 4	Day 6	Day 9	Day 14	Day 21
Placebo	17	17	17	16	15	13	12
S-217622 125 mg	15	15	15	15	14	15	14
S-217622 250 mg	14	14	14	14	13	12	11

Number of patients	Baseline	Day 2	Day 4	Day 6	Day 9	Day 14	Day 21
Placebo	14	14	14	13	13	11	10
S-217622 125 mg	15	15	15	15	14	15	15
S-217622 250 mg	14	14	14	14	13	12	11

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

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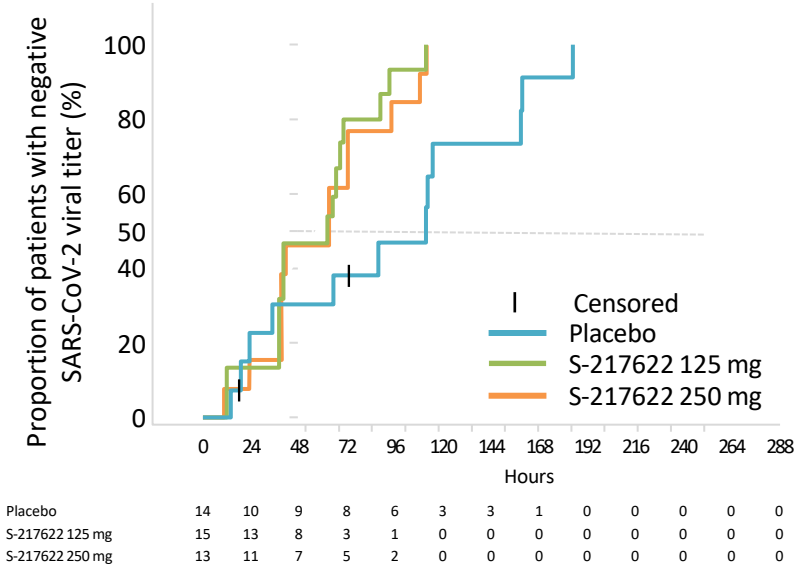
Secondary endpoint: time to the first negative viral titer (mITT)

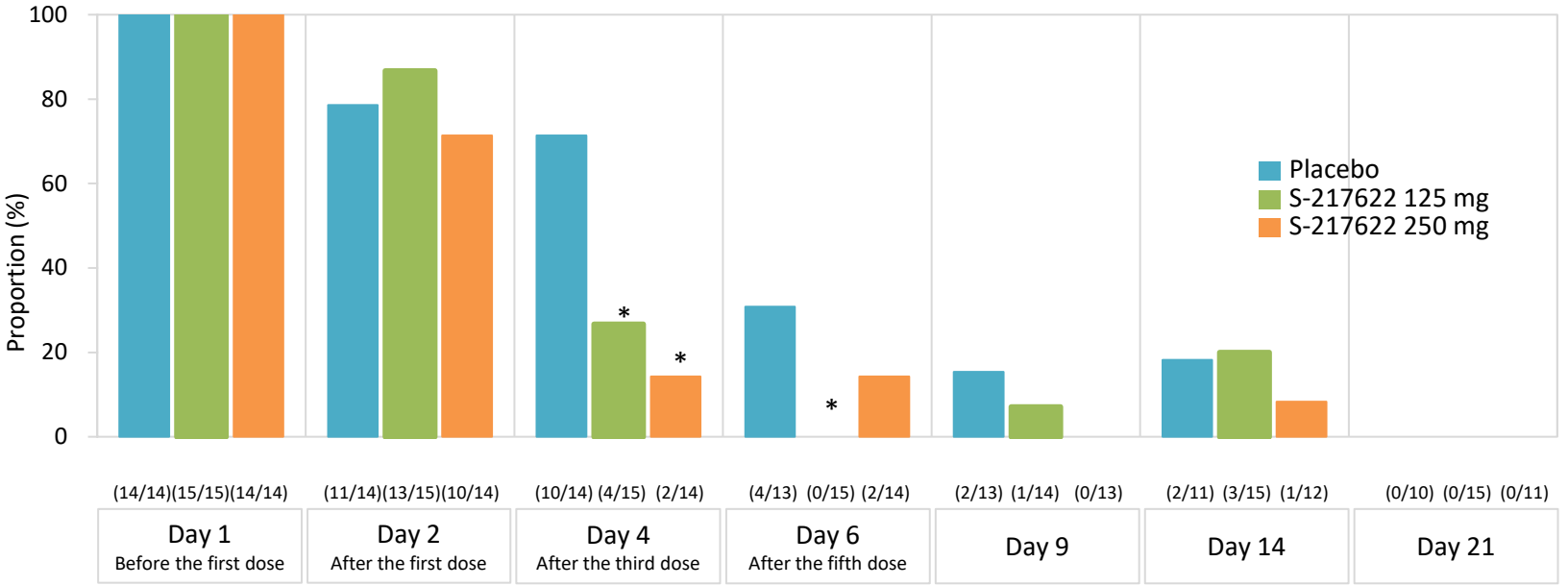


	S-217622 125 mg (n=15)	S-217622 250 mg (n=13)	Placebo (n=14)
Time to negative viral SARS-CoV-2 titer, hours	61.3 (38.0, 68.4)	62.7 (39.2, 72.3)	111.1 (23.2, 158.5)
Difference vs. placebo	−49.8 (−96.7, 30.9)	−48.4 (−95.9, 28.5)	–
P-value[a]	0.0159	0.0205	–

Data are median (95% CI).
[a]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. [a]>0.8 $\log_{10}(TCID_{50}/mL)$. *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; $TCID_{50}$, 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 (%)
Number of participants with any TEAE	11 (52.4)	16 (69.6)	9 (37.5)
TEAE leading to discontinuation of study intervention	0	0	0
TEAE reported in ≥5% of patients in any group			
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)
Subjects with any Treatment-related TEAE	5 (23.8)	10 (43.5)	0
Treatment-related TEAE reported in ≥5% of patients in any group			
HDL Cholesterol decreased	3 (14.3)	8 (34.8)	0
TG increased	0	2 (8.7)	0
Serious adverse event	0	0	0

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

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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

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Appendix

HDL Cholesterol, Triglycerides in Ph2a