Phase 2b part of S-217622, a novel 3C-like protease inhibitor as once daily oral treatment for SARS-CoV-2 infection in Japan and South Korea

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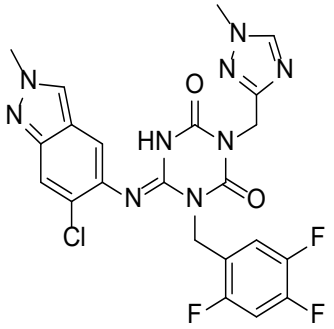
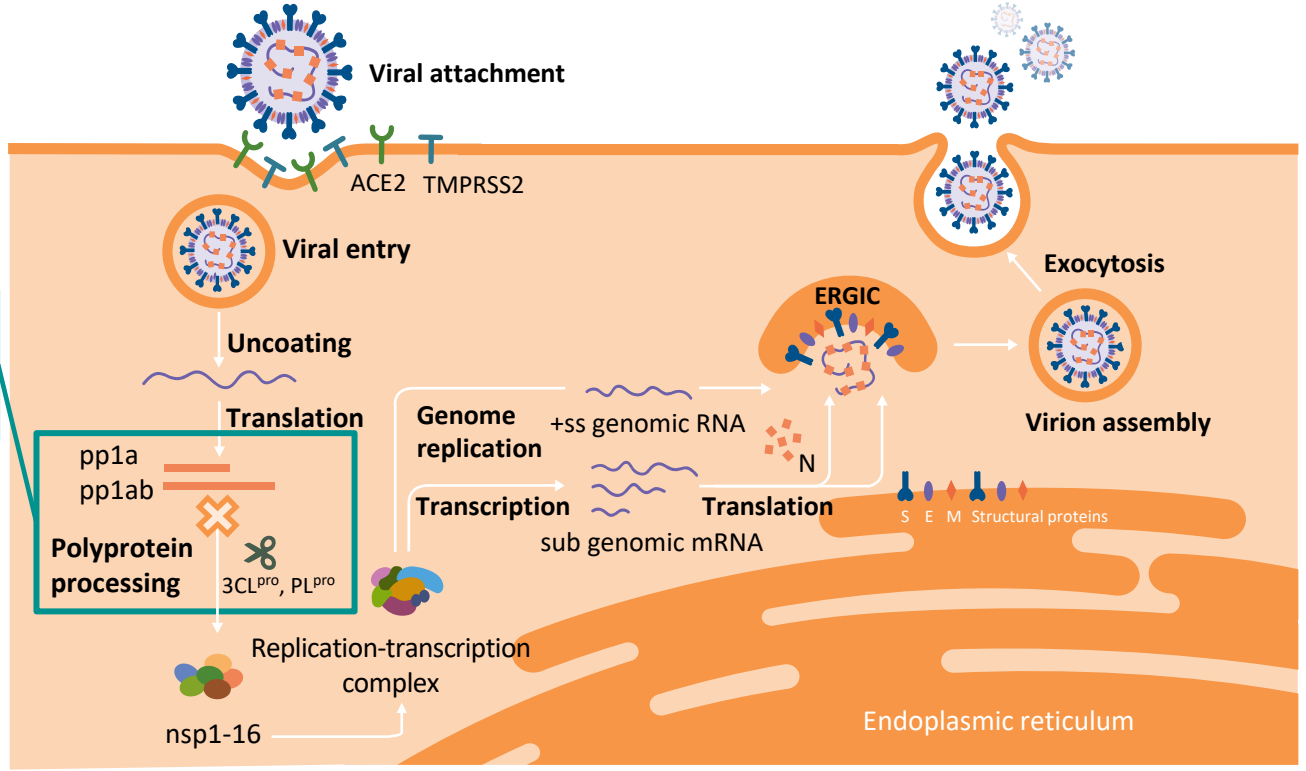
Transparency declaration

- I am a member of S-217622 Advisory Board.

3CL^{pro} is a key enzyme in the viral replication

3CL^{pro} inhibitor S-217622





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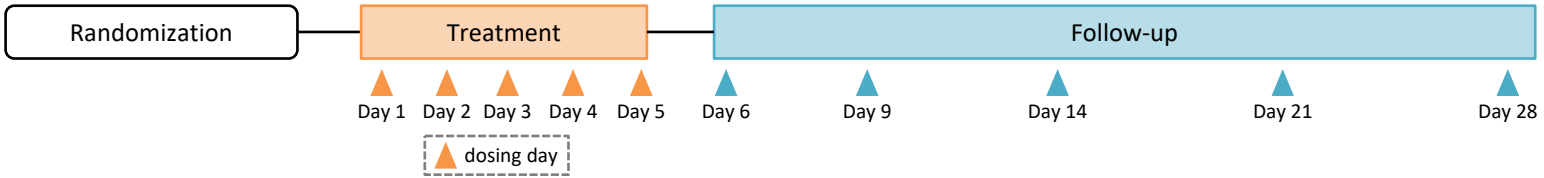
3CL^{pro}, 3C-like protease; ACE2, angiotensin-converting enzyme 2; E, envelope; ERGIC, endoplasmic-reticulum-Golgi intermediate compartment; M, membrane; mRNA, messenger RNA; N, nucleocapsid; nsp1-16, non-structural proteins 1-16; PL^{pro}, papain-like protease; pp1a/1ab, polyprotein 1a/1ab; RdRp, RNA-dependent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

Phase 2b part outline

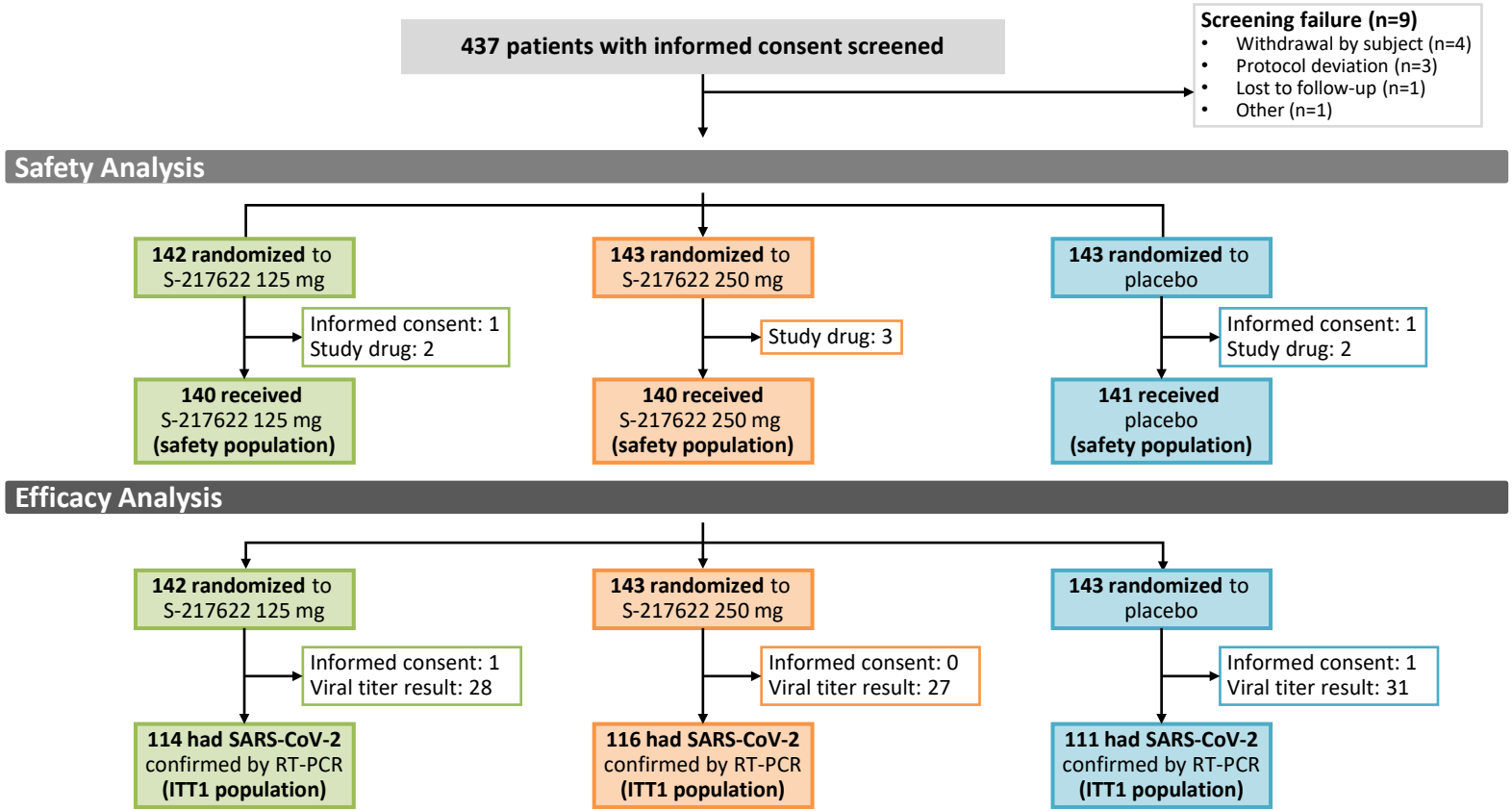
Subjects	Mild/moderate symptoms SARS-CoV-2-infected subjects
Clinical trial design	Multicenter, randomized, placebo-controlled, double-blinded study
Endpoints	Virologic response, clinical symptom, safety
Age	12 to 70 years old
Sample size	435
Dosage and administration	Oral administration of S-217622 or placebo tablet q.d. for 5 days, loading dose at Day 1 followed by 4-days maintenance doses
Group	S-217622 375/125 mg, S-217622 750/250 mg or placebo

Inclusion criteria

- 12 to 70 years of age, at the time of signing the informed consent/assent
- Subjects who were diagnosed as SARS-CoV-2 positive and had COVID-19 onset within 120 hours before randomization
- Subjects who have at least one moderate (COVID-19 score: 2) symptom among the 12 COVID-19 symptoms at enrollment



Patient disposition



ITT1, intent-to-treat 1; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Patient demographics and baseline characteristics

ITT1 Population		S-217622 125 mg (n=114), n (%)	S-217622 250 mg (n=116), n (%)	Placebo (n=111), n (%)
Sex	Male	61 (53.5)	66 (56.9)	72 (64.9)
Age	Mean (SD)	35.6 (13.5)	35.3 (13.1)	37.3 (12.6)
	≥12 to <18	4 (3.5)	2 (1.7)	2 (1.8)
	≥18 to <65	109 (95.6)	112 (96.6)	108 (97.3)
	≥65 to <70	1 (0.9)	2 (1.7)	1 (0.9)
Time from onset to randomization	<24 hours	11 (9.6)	2 (1.7)	5 (4.5)
	≥24 to <48 hours	21 (18.4)	21 (18.1)	24 (21.6)
	≥48 to <72 hours	23 (20.2)	30 (25.9)	25 (22.5)
	≥72 to <96 hours	37 (32.5)	38 (32.8)	33 (29.7)
	≥96 to ≤120 hours	22 (19.3)	23 (19.8)	24 (21.6)
	>120 hours	0	2 (1.7)	0
Vaccination of SARS-CoV-2	Yes	97 (85.1)	97 (83.6)	97 (87.4)
	No	17 (14.9)	19 (16.4)	14 (12.6)

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation

Patient demographics and baseline characteristics (cont'd)

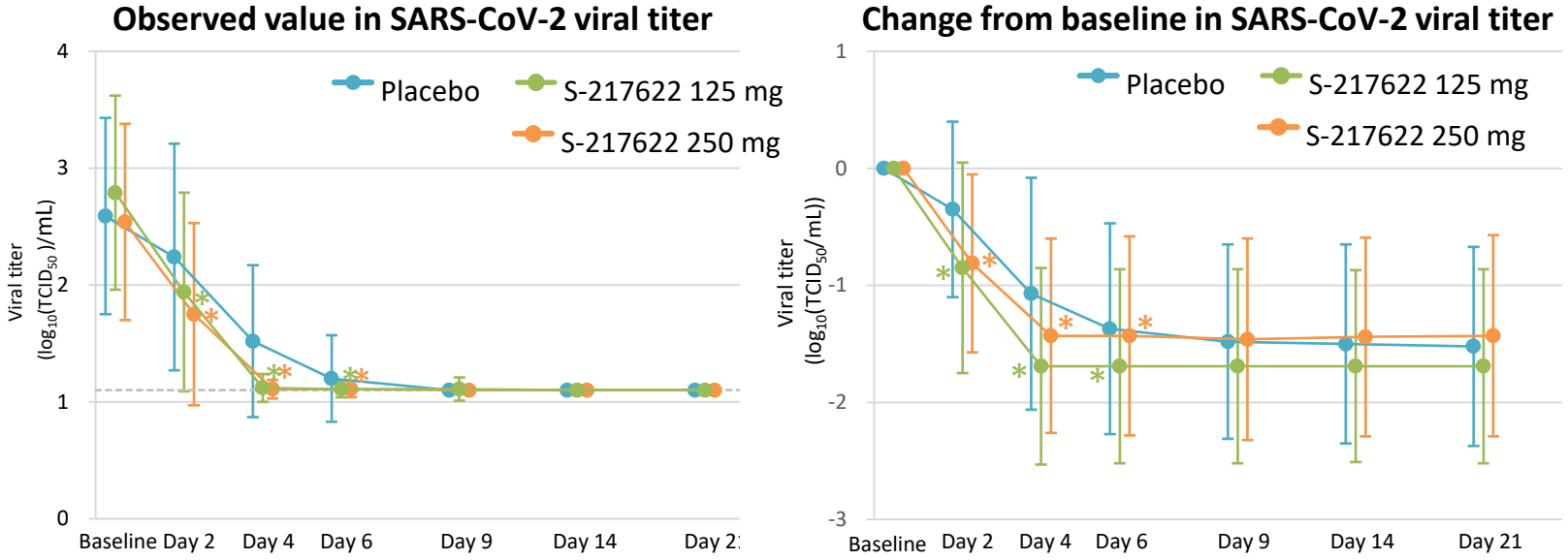
			S-217622 125 mg (n=114), n (%)	S-217622 250 mg (n=116), n (%)	Placebo (n=111), n (%)
COVID-19 symptoms	**Respiratory symptoms**	Stuffy or runny nose	29 (25.4)	34 (29.3)	26 (23.4)
		Sore throat	65 (57.0)	63 (54.3)	54 (48.6)
		Shortness of breath	8 (7.0)	8 (6.9)	1 (0.9)
		Cough	48 (42.1)	46 (39.7)	49 (44.1)
	Systemic symptoms	Low energy or tiredness	37 (32.5)	42 (36.2)	27 (24.3)
		Muscle or body aches	26 (22.8)	19 (16.4)	23 (20.7)
		Headache	28 (24.6)	30 (25.9)	24 (21.6)
		Chills or shivering	31 (27.2)	20 (17.2)	17 (15.3)
		Feeling hot or feverish	43 (37.7)	41 (35.3)	36 (32.4)
	Digestive symptoms	Nausea	4 (3.5)	5 (4.3)	2 (1.8)
		Vomiting	3 (2.6)	3 (2.6)	2 (1.8)
		Diarrhea	6 (5.3)	6 (5.2)	8 (7.2)
	Sensation disturbance	Anosmia	16 (14.0)	10 (8.6)	10 (9.0)
		Dysgeusia	19 (16.7)	7 (6.0)	9 (8.1)

Primary endpoint: Viral titer change from baseline by Day 4 (ITT1)

Statistics	S-217622 125 mg (n=114)	S-217622 250 mg (n=116)	Placebo (n=111)
n	106	112	107
Mean (SD)	–1.69 (0.84)	–1.43 (0.83)	–1.06 (0.99)
LS mean (SE) by ANCOVA[a]	–1.49 (0.04)	–1.49 (0.04)	–1.08 (0.04)
Difference in LS means vs. placebo (SE)	–0.41 (0.05)	–0.41 (0.05)	---
95% CI for difference	–0.51, –0.31	–0.51, –0.31	---
p-value	<0.0001	<0.0001	---

[a]ANCOVA, Analysis of Covariance; CI, Confidence Interval; LS, Least Squares;
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2;
SD, standard deviation; SE, standard error; UNIT, $TCID_{50}$, 50% tissue culture infectious dose

Secondary endpoint: change from baseline in viral titer by time (ITT1)



Mean ± standard deviation:

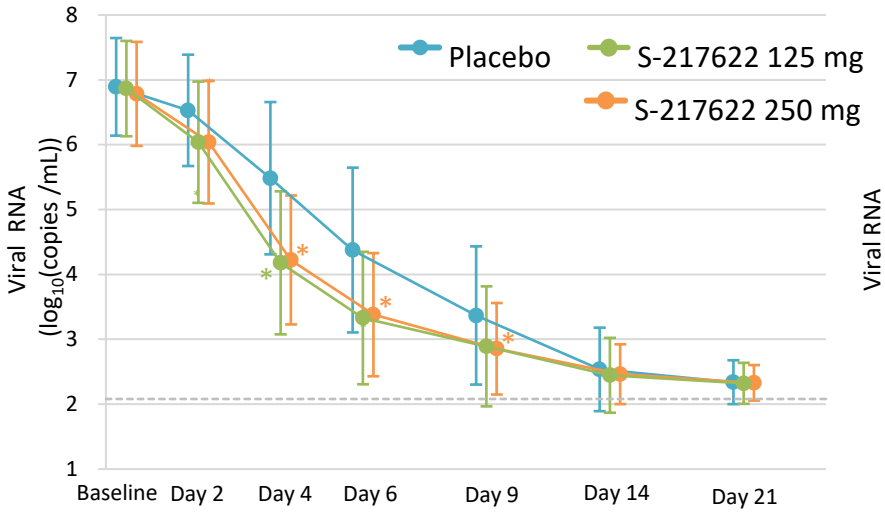
*p<0.05 vs placebo group

Lower limit of detection (1.1 $\log_{10}$ $TCID_{50}$/mL)

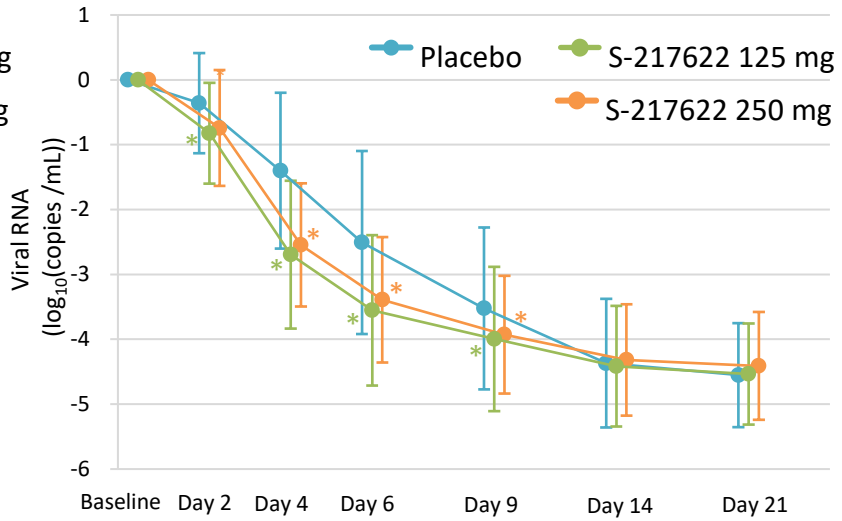
ANCOVA, Analysis of Covariance; Covariate: SARS-CoV-2 viral titer at baseline, time from onset to randomization [<72 hours or ≥72 hours], SARS-CoV-2 vaccination history [Yes or No]

Secondary endpoint: change from baseline in viral RNA by time (ITT1)

Observed value in SARS-CoV-2 viral RNA



Change from baseline in SARS-CoV-2 viral RNA



Mean ± Standard deviation:

*p<0.0001 vs placebo group

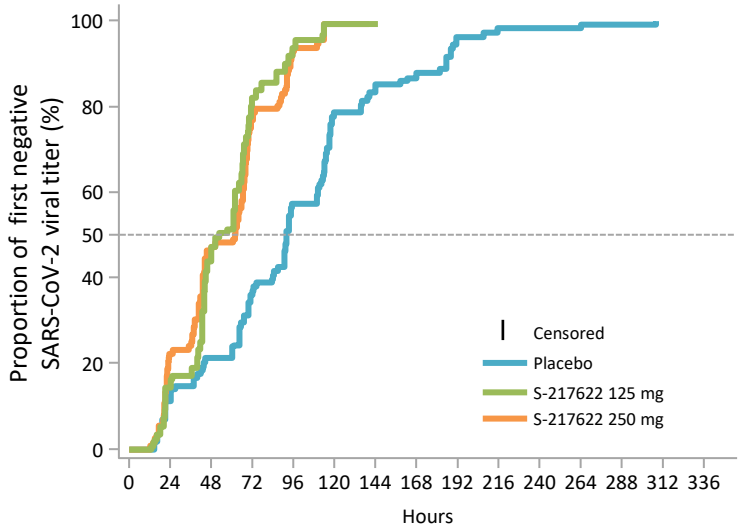
Lower limit of quantification (2.08 $\log_{10}$ copies/mL)

ANCOVA, Analysis of Covariance; Covariate: SARS-CoV-2 viral RNA at baseline, time from onset to randomization [<72 hours or ≥72 hours], SARS-CoV-2 vaccination history [Yes or No]

If viral RNA is negative and less than the lower limit of quantification, the viral RNA was imputed by 2.27 and 2.08 $\log_{10}$ copies/mL, respectively.

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Secondary endpoint: time to the first negative viral titer (ITT1)



Placebo	108	95	85	69	46	23	17	14	4	3	2	2	1	0	0
S-217622 125 mg	111	93	58	20	7	1	1	0	0	0	0	0	0	0	0
S-217622 250 mg	113	87	59	26	8	1	0	0	0	0	0	0	0	0	0

	S-217622 125 mg (n=111)	S-217622 250 mg (n=113)	Placebo (n=108)
Median [95% CI]	51.3 [44.1, 61.8]	62.1 [43.7, 66.5]	91.9 [84.0, 109.9]
Difference vs. placebo [95% CI]	–40.6 [–8.5, –26.5]	–29.8 [–52.0, –23.6]	---
P-value[a]	<0.0001	<0.0001	---

[a]Stratified log-rank test vs. placebo
Adjusted by the following strata (time from onset to randomization [<72 hours or ≥72 hours], SARS-CoV-2 vaccination history [Yes or No])

One patient in the S-217622 250 mg was excluded owing to use of a prohibited concomitant drug on Day 1.
CI, confidence interval; ITT1, intent-to-treat 1; q.d., once daily; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Primary endpoint: Change from baseline in 12 COVID-19 symptoms Total Score (ITT)

Statistics	S-217622, 125 mg (n=114)	S-217622, 250 mg (n=116)	Placebo (n=111)
n	109	113	110
Mean (SD)	–5.95 (4.02)	–5.42 (3.70)	–4.92 (3.25)
LS mean (SE) by ANCOVA[a]	–5.37 (0.24)	–5.17 (0.23)	–5.12 (0.24)
Difference in LS means vs. placebo (SE)	–0.24 (0.30)	–0.04 (0.29)	---
95% CI for difference	–0.83, 0.34	–0.62, 0.53	---
p-value	0.4171	0.8806	---

[a]Covariate: Total score of COVID-19 symptoms at baseline, time from onset to randomization [<72 hours or ≥72 hours], SARS-CoV-2 vaccination history [Yes or No]
ANCOVA, Analysis of Covariance; CI, Confidence Interval; LS, Least Squares; SD, standard deviation; SE, standard error

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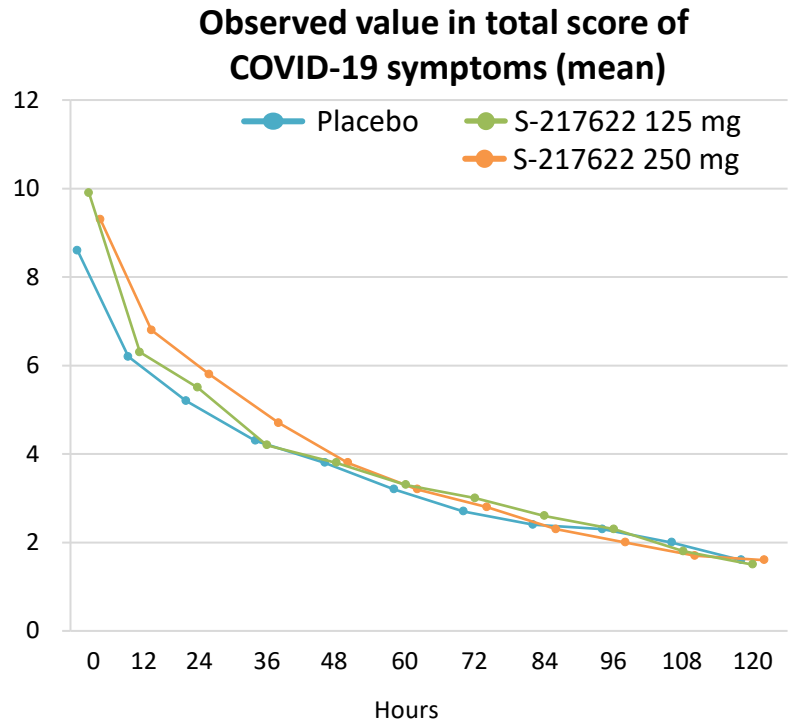
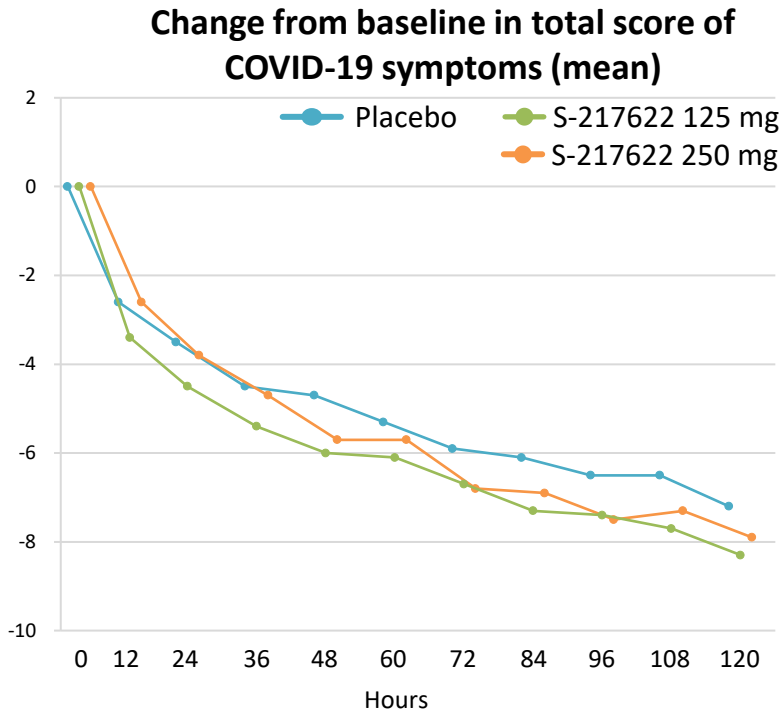
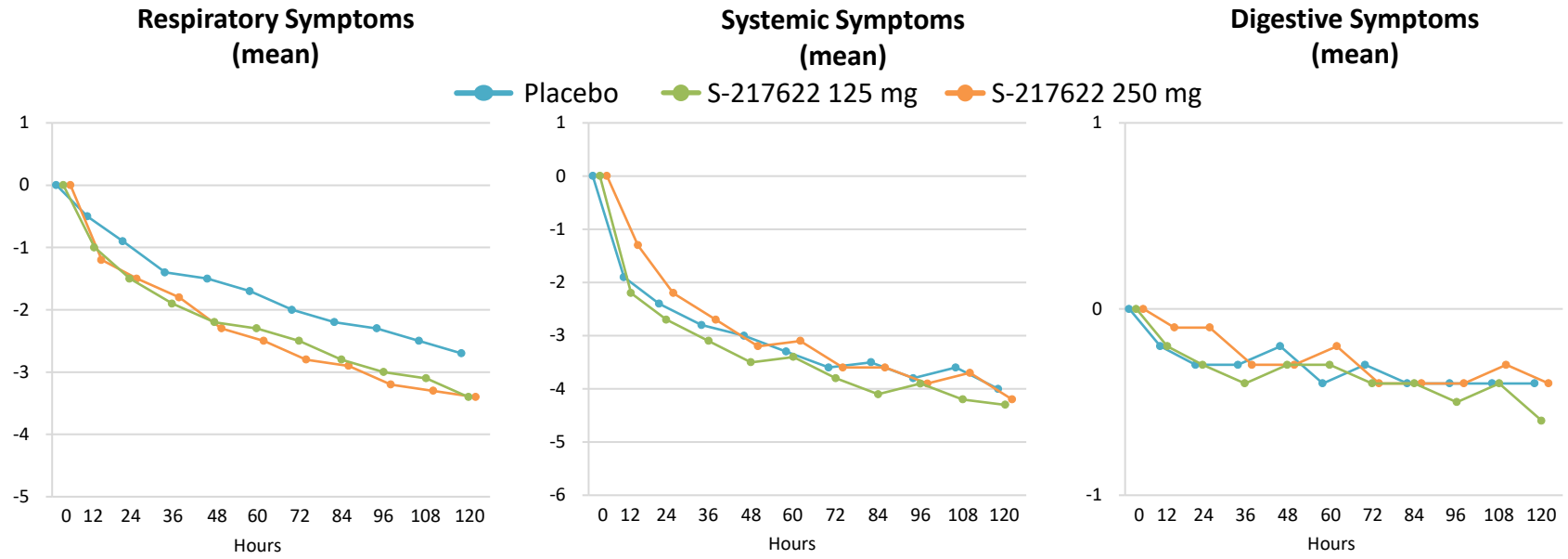
Change in 12 COVID-19 symptoms Total Score by time (ITT)





Change in Subtotal Score of COVID-19 symptoms (ITT)

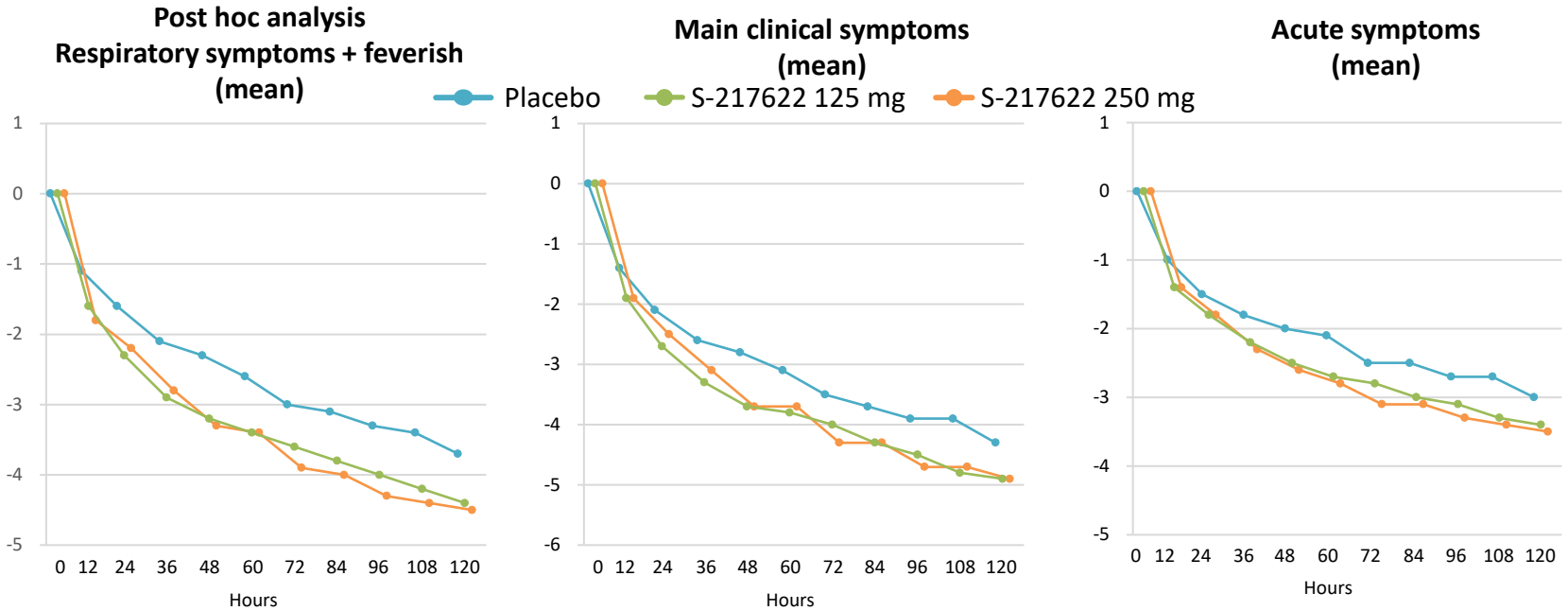


Respiratory symptoms: stuffy or runny nose, sore throat, shortness of breath, cough

Systemic Symptoms: Low energy or tiredness, Muscle or body aches, Headache, Chills or shivering, Feeling hot or feverish

Digestive Symptoms: Nausea, Vomiting, Diarrhea

Change in Subtotal Score of COVID-19 symptoms (ITT)



Respiratory and feverish symptoms: stuffy or runny nose, sore throat, shortness of breath, cough, feeling hot or feverish

Acute symptoms: sore throat, cough, feeling hot or feverish

Main clinical symptoms: stuffy or runny nose, sore throat, cough, chills or shivering, feeling hot or feverish

Safety

	S-217622 125 mg (n=140) n (%)	S-217622 250 mg (n=140) n (%)	Placebo (n=141) n (%)
Number of participants with any TEAEs	48 (34.3)	60 (42.9)	44 (31.2)
TEAE reported in ≥2% of patients in any group			
Dyslipidemia	0	3 (2.1)	0
Headache	3 (2.1)	3 (2.1)	0
Diarrhea	2 (1.4)	3 (2.1)	1 (0.7)
Abdominal pain (upper)	0	0	4 (2.8)
Rash	2 (1.4)	1 (0.7)	3 (2.1)
Back pain	1 (0.7)	3 (2.1)	1 (0.7)
High-density lipoprotein cholesterol decreased	31 (22.1)	40 (28.6)	5 (3.5)
Blood triglycerides increased	1 (0.7)	9 (6.4)	1 (0.7)
Blood creatine phosphokinase increased	0	0	4 (2.8)
Subjects with any Treatment-related TEAE	19 (13.6)	31 (22.1)	7 (5.0)
Treatment-related TEAE reported in ≥5% of patients in any group			
High-density lipoprotein cholesterol decreased	13 (9.3)	22 (15.7)	0

Summary and Conclusions

- Phase 2b was conducted to assess S-217622 efficacy and safety in patients with mild/moderate COVID-19 symptoms during the Omicron epidemic
- S-217622 demonstrated significant reduction and rapid clearance of infectious SARS-CoV-2
- No clear difference was observed in total score of 12 symptoms between S-217622 and placebo
  - S-217622 suggested a favorable trend of improvement in subtotal symptom score of “respiratory and feverish”
- S-217622 was well tolerated
- Ongoing Phase 3 studies will provide further virology and clinical evidence of S-217622 as an oral treatment for COVID-19
  - SCORPIO-SR: patients with mild/moderate COVID-19 symptoms
  - SCORPIO-HR: patients with risk factors for severe complications

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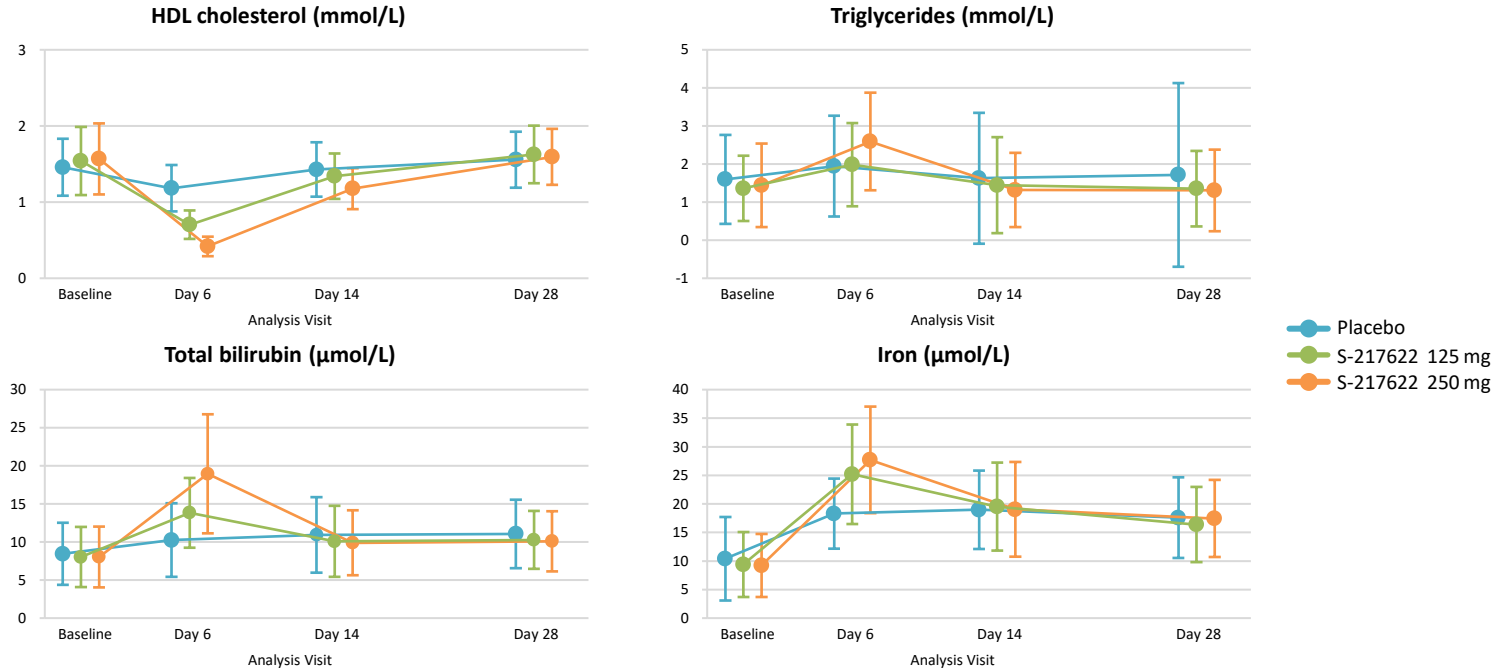
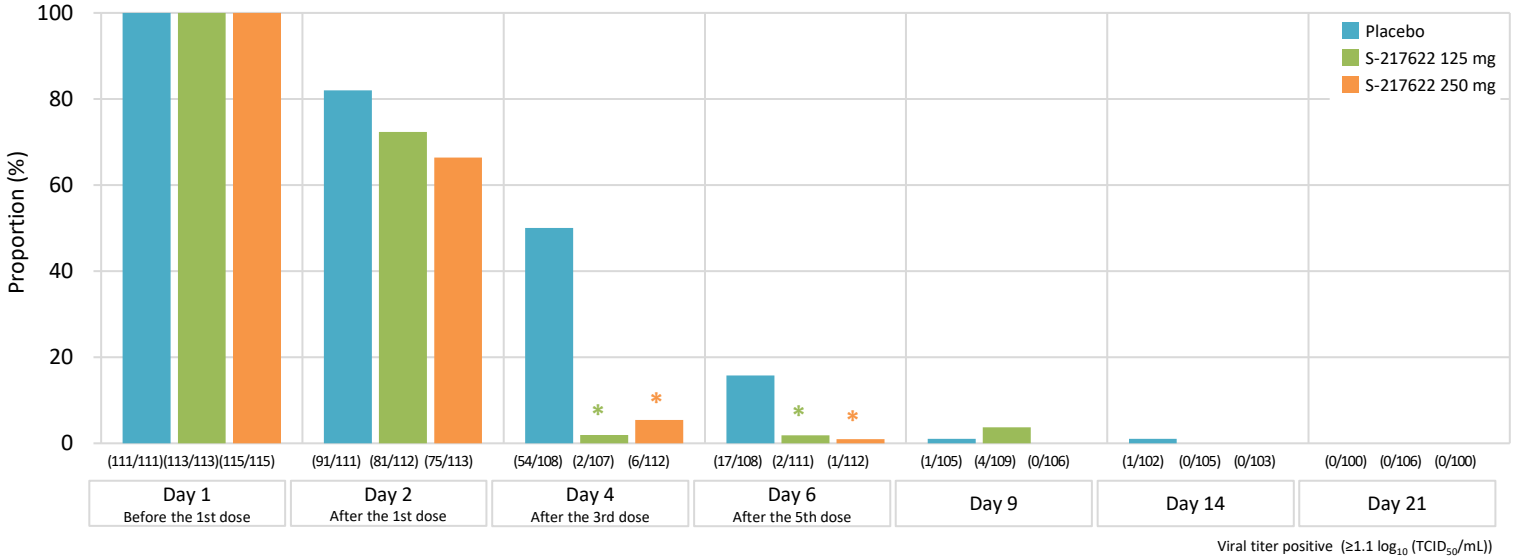
Changes in HDL cholesterol, Triglycerides, Total bilirubin and Iron in Blood



HDL, high-density lipoprotein

Secondary endpoint: proportion of patients with a positive viral titer (ITT1)



[A] >1.1 $\log_{10}$($TCID_{50}$ /mL). *p<0.05 vs placebo group.
Mantel-Haenszel test vs placebo adjusted by the following strata (time from onset to randomization [<72 hours or ≥72 hours], SARS-CoV-2 vaccination history [Yes or No])
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.
ITT1 population: Patients with positive baseline viral titer.
ITT1, intent-to-treat1; q.d., once daily; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; $TCID_{50}$, 50% tissue culture infectious dose