Top-Line Results of the Phase 2a Part of the Phase 2/3 Trial of S-217622, the COVID-19 Therapeutic Drug

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Phase 2a Part（of Phase 2/3 trial）

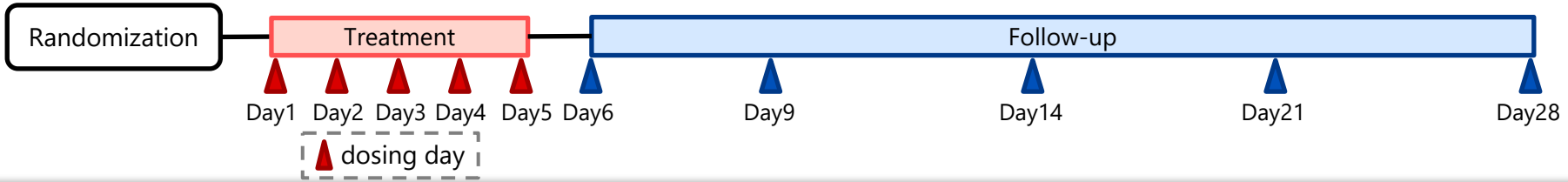
Subjects	Mild/moderate and asymptomatic/only mild symptoms SARS-CoV-2-infected subjects
Clinical trial design	Multicenter, randomized, placebo-controlled, double-blind study
Endpoints	Efficacy, Safety
Age	12 to 70 years old
Sample size	69
dosage and administration	Oral administration of S-217622 or placebo tablet once daily for 5 days (5 times in total)
group	low dose, high dose, placebo

Mild/moderate and asymptomatic/only mild symptoms SARS-CoV-2-infected subjects

＜Common 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 within 120 hours before randomization.

＜Subjects with mild/moderate SARS-CoV-2 infection＞
- Subjects with time from COVID-19 onset to randomization of =< 120 hours
- Subjects who have at least one moderate (COVID-19 score: 2) or severe symptom among the following 12 COVID-19 symptoms at enrollment (excluding symptoms present prior to COVID-19 onset)

＜Subjects with asymptomatic/only mild symptoms SARS-CoV-2 infection＞
- Subjects who have none of the symptoms of COVID-19 within 2 weeks before randomization, or mild symptoms only SARS-CoV-2 infection



* An event that causes sufficient discomfort and interferes with normal everyday activities

Main Endpoints

Efficacy analysis	**【Antiviral effect】→ Primary endpoint** Change from baseline in SARS-CoV-2 viral titer at each time point （Viral titer: Amount of infectious virus (living virus) contained in the sample）
	【Antiviral effect】 • Change from baseline in SARS-CoV-2 viral RNA at each time point （Viral RNA: Amount of viral RNA (including fragments of the dead virus genome) contained in the sample） • Proportion of patients with viral titer positivity at each time point • Time to first confirmation of negative SARS CoV-2 viral titer
	【Clinical Symptom improvement】 • Mean Change from Baseline in COVID-19 Symptom Score at each time point
	【Effect in preventing exacerbation】 • Proportion of first exacerbated subjects with 3 or higher on 8-Point Ordinal Scale* score at any point after the treatment (exploratory analysis) * Scale that classifies clinical severity into 8 levels
Safety analysis	• Treatment-emergent adverse events (TEAE) / Treatment-related TEAE

Key Demographics of Subjects

Background information in the ITT* population

		low dose N=16	high dose N=14	placebo N=17
Sex	Male	8	8	13
	Female	8	6	4
Age	Min	22	23	16
	Max	59	63	61
Severity	mild/moderate	14	12	14
	asymptomatic/ only mild	2	2	3
Vaccination of SARS-CoV-2	Yes	14 (87.5%)	12 (85.7%)	12 (70.6%)
	No	2	2	5

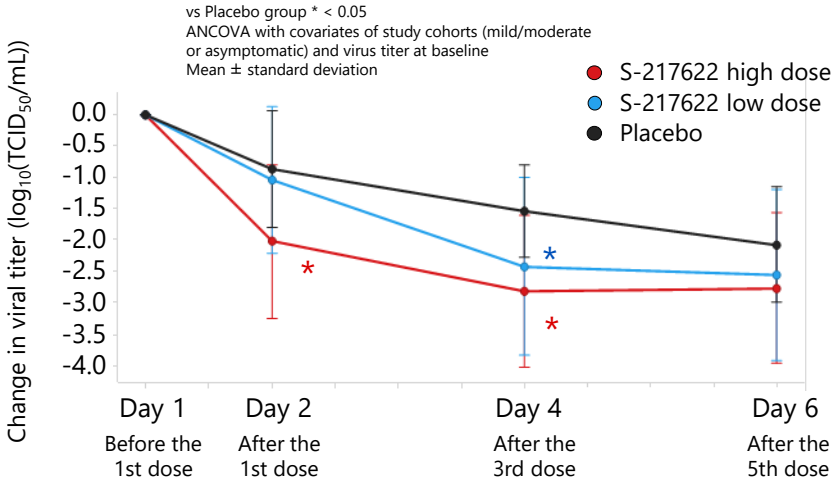
* Intention-to-treat (ITT): All subjects who were randomly assigned to the study intervention and had a SARS-CoV-2 infection based on RT-PCR. 47 subjects excluding 22 subjects that were PCR negative at baseline from 69 subjects

Efficacy

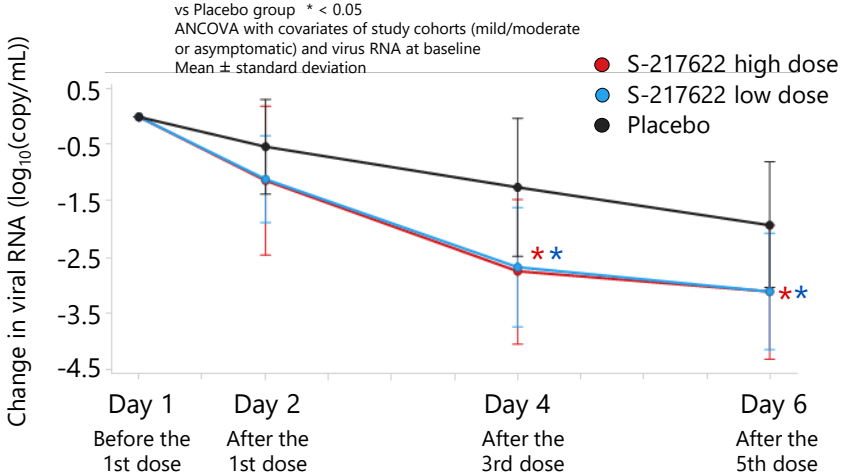
- Antiviral effect (Viral titer/RNA)
- Clinical Symptom improvement
- Effect in preventing exacerbations

Antiviral Effect: Viral Titer, Viral RNA

Mean change from baseline in viral titer



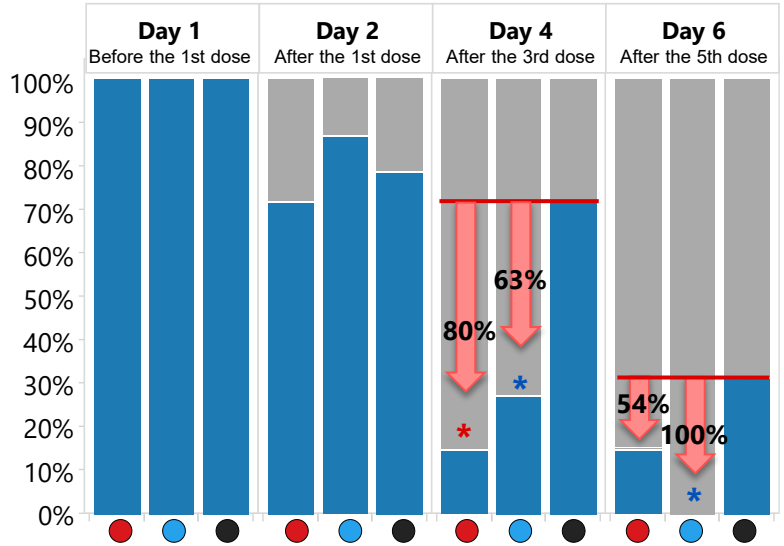
Mean change from baseline in amount of viral RNA



Rapid reduction in viral titer and viral RNA compared to placebo group

Antiviral Effect: Proportion of Patients with Positive Viral Titer

Proportion of patients with viral titer positivity



vs Placebo group *< 0.05
Mantel-Haenszel test stratified by study cohorts (mild/moderate or asymptomatic)

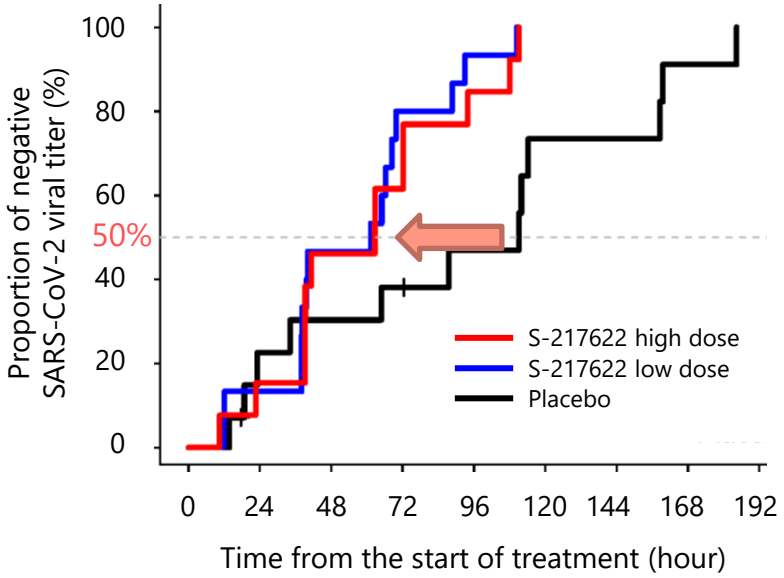
- S-217622 high dose
- S-217622 low dose
- Placebo

- **On day 4 (After the 3rd dose), the proportion of patients with positive viral titer decreased by approximately 60-80% compared to the placebo group**

S-217622 rapidly reduces the number of subjects shedding infectious virus

Antiviral Effect: Time to the First Negative SARS-CoV-2 Viral Titer

Kaplan-Meier Plot for time to the First Negative SARS-CoV-2 Viral Titer



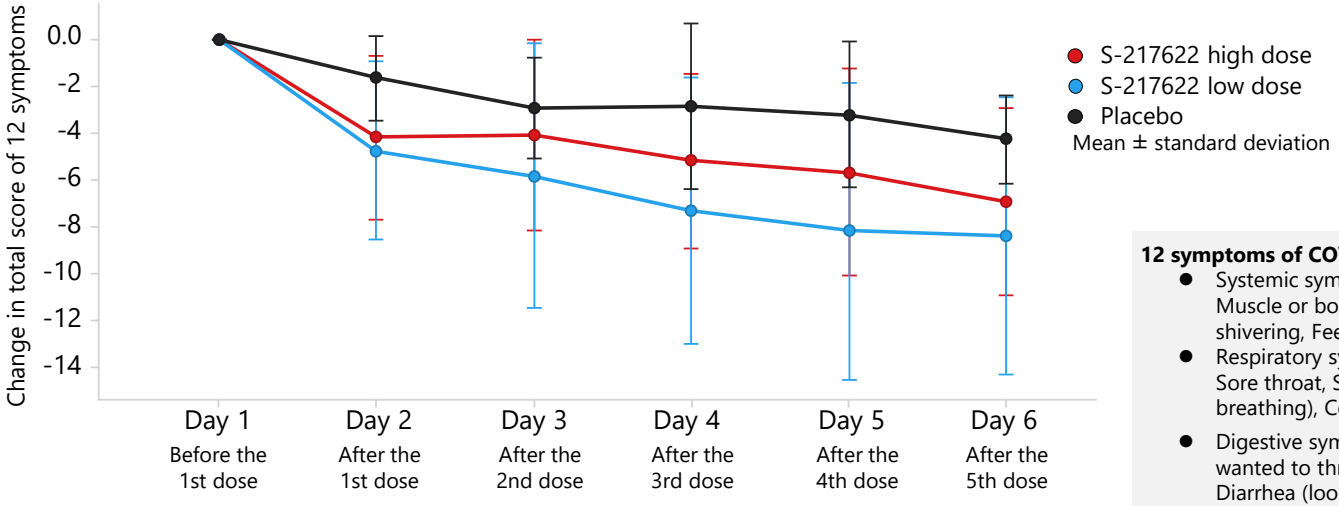
	S-217622: low dose N = 15	S-217622: high dose N = 13	Placebo N = 14
Median (hours) [95% CI*]	**61.3** [38.0, 68.4]	**62.7** [39.2, 72.3]	**111.1** [23.2, 158.5]
Difference [95% CI*]	**-49.8** [-96.7, 30.9]	**-48.4** [-95.9, 28.5]	---
Stratified log-rank test**	P = 0.0159	P = 0.0205	---

* CI= Conference Interval
** Log-rank test stratified by study cohorts (mild/moderate or asymptomatic/only mild symptoms)

Median time to the negative SARS-CoV-2 viral titer shortened by 2 days compared to the placebo group

Clinical improvement: Change from Baseline in COVID-19 Symptom Score

Mean change from baseline in 12 COVID-19 symptom total score



12 symptoms of COVID-19

- Systemic symptoms: Low energy or tiredness, Muscle or body aches, Headache, Chills or shivering, Feeling hot or feverish
- Respiratory symptoms: Stuffy or runny nose, Sore throat, Shortness of breath (difficulty breathing), Cough, Low energy or tiredness
- Digestive symptoms: Nausea (feeling like you wanted to throw up), Vomiting (throw up), Diarrhea (loose or watery stools)

- **Confirmed a tendency toward improvement in total score of 12 COVID-19 symptoms, and further analysis will be continued with subjects enrolled in the subsequent part of the trial**

Effect in preventing exacerbations

8-Point Ordinal Scale* exacerbation rate (exploratory analysis)

(Proportion of first exacerbated subjects with 3 or higher on 8-Point Ordinal Scale* score at any point after the treatment)

⇒Proportion of subjects whose condition worsened after the treatment and was judged by the physician to be hospitalized or to be treated equivalent to hospitalization

	S-217622: low dose	S-217622: high dose	Placebo
Proportion of subject with 3 or higher on ordinal scale score	**0.0%**	**0.0%**	**14.3%**
Number of subjects	0/13	0/12	2/14

8-Point Ordinal Scale	Score
Asymptomatic	0
Symptomatic, no limitation of activities	1
Symptomatic, limitation of activities	2
Hospitalized, no oxygen therapy	3
Hospitalized, with oxygen therapy (< 5 L/min)	4
Hospitalized, with oxygen therapy (≥ 5 L/min)	5
Hospitalized, with ventilation	6
Death	7

No subject with 3 or higher on the 8-Point Ordinal Scale score in the S-217622 group

* Scale that classifies clinical severity into 8 levels

Safety

Treatment-emergent adverse events (TEAE) / Treatment-related TEAE

Treatment-emergent adverse events (TEAE)

	S-217622: low dose N = 21	S-217622: high dose N = 23	Placebo N = 24
Subjects with any TEAE	11	16	9
Percentage of subjects	52.4%	69.6%	37.5%

Treatment-related TEAE

	S-217622: low dose N = 21	S-217622: high dose N = 23	Placebo N = 24
Subjects with any TEAE	5	10	0
Percentage of subjects	23.8%	43.5%	0.0%

- **No high-grade or serious TEAE have been observed**
- **No TEAE resulting in discontinuation have been observed**

1 patient with no study drug administered is excluded from the safety analysis

Treatment-emergent adverse events (TEAE) （5% or more）

Treatment-emergent adverse events (TEAE)
(5% or more)

	S-217622: low dose N = 21	S-217622: high dose N = 23	Placebo N = 24
Subjects with any TEAE (Percentage of subjects)	**11（52.4%）**	**16（69.6%）**	**9（37.5%）**
Nasopharyngitis	2（9.5%）	0	0
Headache	1（4.8%）	3（13.0%）	0
Rhinalgia	2（9.5%）	0	0
High density lipoprotein (HDL) decreased	3（14.3%）	12（52.2%）	2（8.3%）
Blood triglycerides (TG) increased	0	3（13.0%）	0
Aspartate aminotransferase (AST) increased	1（4.8%）	1（4.3%）	2（8.3%）
Blood bilirubin increased	0	2（8.7%）	0
Alanine aminotransferase increased (ALT)	1（4.8%）	0	2（8.3%）

Treatment-related TEAE (5% or more)

Treatment-related TEAE (5% or more)

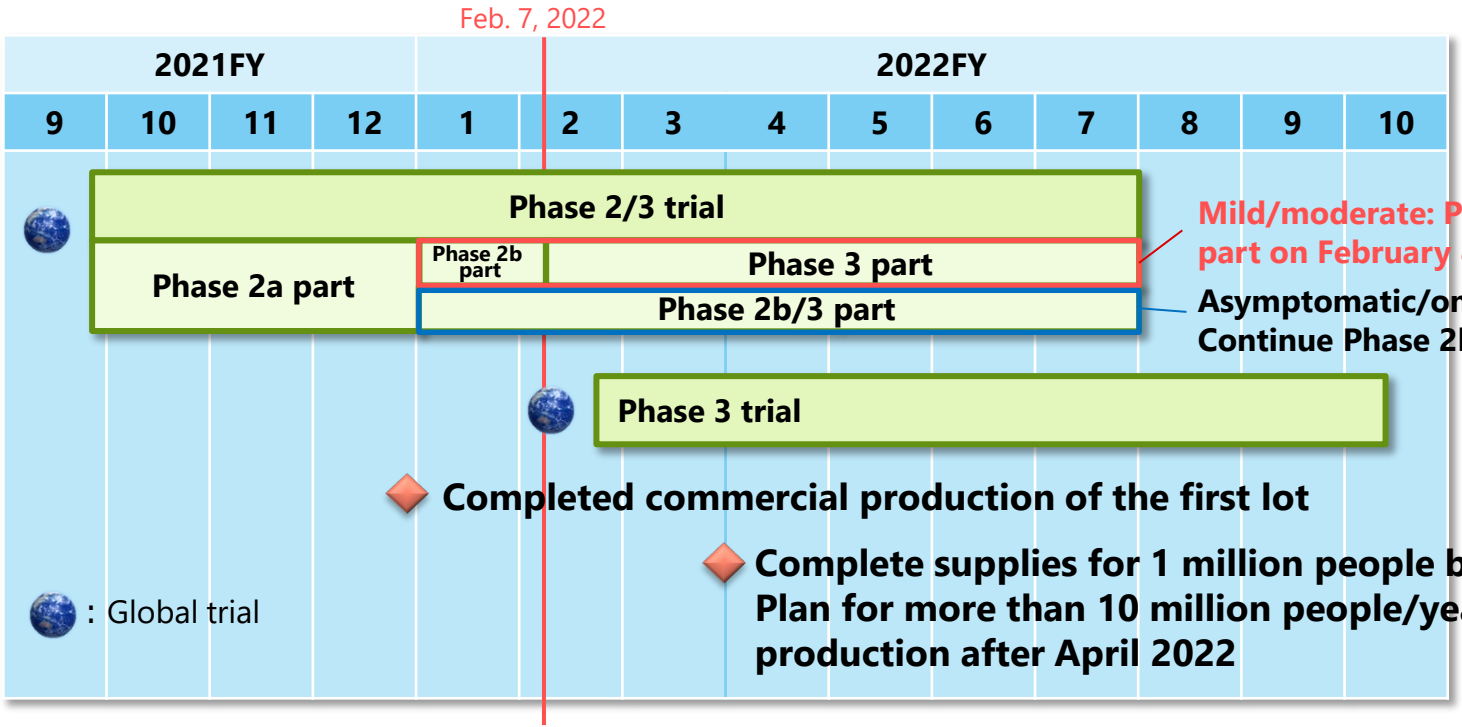
	S-217622: low dose N = 21	S-217622: high dose N = 23	Placebo N = 24
Subjects with any treatment-related TEAE (percentage of subjects)	**5（23.8%）**	**10（43.5%）**	**0**
High density lipoprotein (HDL) decreased	3（14.3%）	8（34.8%）	0
Blood triglycerides (TG) increased	0	2（8.7%）	0

- **Almost all TEAE were mild and all treatment-related TEAE were mild**
- **HDL decreases and TG increases were observed in the Phase 1 trial, and safety and recoverability of these events were confirmed in the Phase 1 trial (~2,000mg)**

Summary

- **Antiviral effect**
  - The S-217622 arms showed a significant difference compared to the placebo group with respect to each of the following:
    - > Rapid reductions in viral titer and viral RNA
    - > On day 4, the proportion of subjects with positive viral titer decreased by approximately 60-80% compared to the placebo group
    - > Median time to the negative SARS-CoV-2 viral titer shortened by 2 days compared to the placebo group
- **Clinical Symptom improvement**
  - S-217622 showed a tendency toward improvement in total score of 12 COVID-19 symptoms
    - > There were two subjects with exacerbation of COVID-19 symptoms in the placebo group, but none in the S-217622 group
- **Safety**
  - No high-grade or serious TEAE have been observed
  - No TEAE resulting in discontinuation have been observed
  - Almost all TEAE were mild and all treatment-related TEAE were mild

S-217622：Current Status and Future Plans



Based on favorable results,
we will continue to aim for the fastest domestic provision

Appendix

Nonclinical Efficacy: Activity against Omicron Variant

Activity against omicron variant

In vitro assay using VeroE6T cells

SARS-CoV-2 variant	EC_{50} (μM)	Major mutation site	
		Spike-protein	3CL-protease
WK-521 strain	**0.37**	-	-
α variant (QHN001/QHN002/QK002)	**0.31/0.46/0.33**	N501Y, D614G	-
β variant (TY8-612)	**0.40**	K417N, E484K, N501Y, D614G	K90R*
Γ variant (TY7-501/TY7-503)	**0.50/0.43**	K417T, E484K, N501Y, D614G	-
δ variant (TY11-927-P1)	**0.41**	L452R, T478K, D614G	-
ο variant (TY38-873)	**0.29**	K417N, K440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H	P132H

Antiviral activity retained across various strains, including the current globally problematic omicron variant

* Inhibitory assessment using K90R enzyme confirmed no effect on drug efficacy

Reference: Mean Change from Baseline in Virus RNA (other antivirals)

		Molnupiravir Phase 2 *1		PAXLOVID HR Phase 3 *2		REGEN-COV HR Phase 3 *3	
		Molnupiravir 800 mg	Placebo	Nirmatrelvir 300 mg ritonavir 100 mg	Placebo	REGEN-COV 2,400 mg	Placebo
Day 3	N	51	56				
	Mean*	-1.050	-0.847				
	Diff* vs placebo	**-0.203**	---				
Day 5	N	52	57	211	240		
	Mean*	-1.867	-1.320	-2.69	-1.75		
	Diff* vs placebo	**-0.547**	---	**-0.93**	---		
Day 7	N	49	56			1355	1341
	Mean*	-2.485	-1.952			-3.32	-2.47
	Diff* vs placebo	**-0.534**	---			**-0.86**	---

* Least square mean

*1 Fischer W. et al. (2021). Molnupiravir, an Oral Antiviral Treatment for COVID-19.
*2 Analyst and Investor Call to Discuss the First COVID-19 Comprehensive Approach: Pfizer-BioNTech Vaccine and Pfizer's Novel Oral Antiviral Treatment Candidate
*3 Weinreich D. M. et al. (2021). REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19.

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