SHIONOGI & CO., LTD.

Briefing Session on COVID-19 Therapeutic Drug S-217622

February 7, 2022

Presentation

Kyokawa: Hello. My name is Kyokawa, and I am the Vice President, Corporate Communications Department at SHIONOGI & CO., LTD. Thank you very much for joining us today.

We will now hold a briefing session on our COVID-19 therapeutic drug, S-217622.

First of all, I would like to introduce today's speakers.

Isao Teshirogi, President and CEO.

Teshirogi: Hello. Thank you.

Kyokawa: Next, I would like to introduce Takuko Sawada, Director and Executive Vice President and Senior Vice President of Integrated disease care Department.

Sawada: This is Sawada. Thank you.

Kyokawa: Lastly, Takeki Uehara, Vice President, Clinical Research Department.

Uehara: This is Uehara. Thank you.

Kyokawa: Today, we would like to begin with an address by Dr. Teshirogi on the results of the Phase 2a part of the Phase 2/3 study of the COVID-19 therapeutic drug, S-217622. This will be followed by a presentation on the details of the results by Dr. Uehara. Afterwards, we will hold a question-and-answer session. The event is scheduled to end at 18:30.

Let's make a start. Over to you, President Teshirogi.

Teshirogi: Hello again. Thank you all for coming.

We only provided data on the virus in a manner that is linked to 3Q financial results. Since you are all familiar in this area, you will understand that we are monitoring safety of all cases up to the 28th day, and the complete database lock was at the end of last week. In this respect, we are presenting the results of the trial today so that we provide some information on symptoms and safety.

With regard to the virus, as was the case with Xofluza, we are very confident that clinical trials are proceeding in a way that demonstrates the power of preclinical studies.

Today We would also like to talk about one of the parameters of efficacy, and more specifically, what impact it may have on symptom progression and severity, as well as safety. We will also provide an overall picture of the status of S-217622.

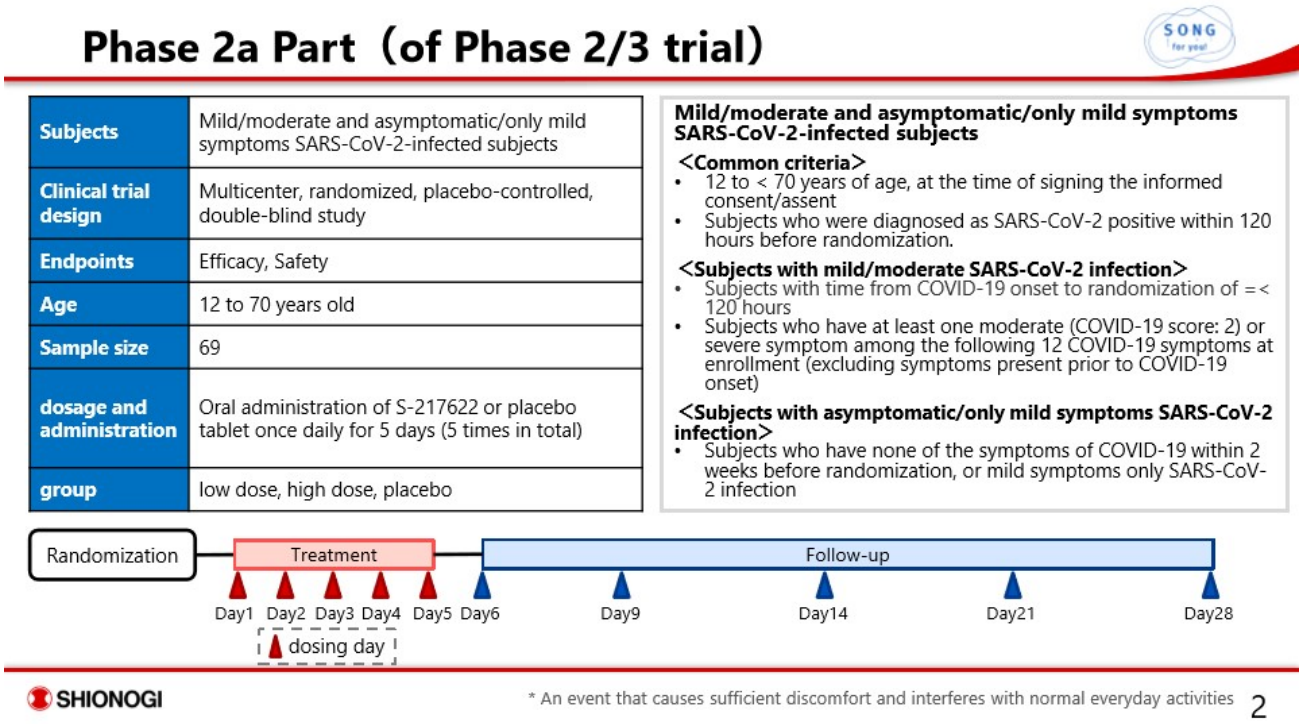
While we are not completely sure how many cases will be included in the final analysis, and we could close it today, we will close the Phase 2b part tomorrow and start the analysis from there.

We have been following the safety of the drug on days 5, 7, and 28 up to this point. This includes placebo and actual drug data. It seems that there is not a large qualitative or quantitative difference in safety between day 28 and day 7. Therefore, we feel that we will be able to get a lot of information about drug efficacy and safety from the day seven safety data observed in Phase 2b part.

With regard to Phase 2b part, we will analyze the virus, symptoms, and safety as soon as possible after the seven-day cutoff. We will move forward with analysis of the Phase 2b part data from the end of next week, aiming for completion at the start of the following week. If the data obtained is in agreement with that obtained in Phase 2a part, we will move toward a conditional approval application. That is our current position.

Dr. Uehara was in charge of Xofluza for a long time, and his expertise includes global clinical trials of antivirals. Dr. Uehara is also in charge of S-217622 development. He will present the data, the details of the trial, its implementation, and discuss his impressions of the current status. Sawada and I will present information regarding the story of the entire company, including global matters.

Thank you.



Uehara: Hello, this is Uehara. I am the global project leader for S-217622. Today, I would like to briefly explain the results of Phase 2a part of the Phase 2/3 trials.

This slide is an outline of the trial.

This is a multicenter, placebo-controlled, double-blind, parallel-group study being conducted in Japan and other Asian countries. This study consists of two cohorts of patients, one with symptoms and the other with no or very mild symptoms. The former is a cohort to study how reduction in viral load is related to symptomatic improvement with this compound. In the latter cohort, we are trying to determine the extent to which the antiviral effect of the drug will prevent the onset of symptoms.

We now have data for a total of 69 patients, mainly from these two cohorts. I would like to talk about the data of these 69 cases.

As you can see from the bottom of the page2, the design of the administration was as follows: repeated oral administration once a day for five days, followed by safety and efficacy follow-up until day 28.

Patients receiving the study drug are those enrolled within 120 hours of onset of COVID-19 infection. One of the features of this trial is that vaccination status is not a criterion for inclusion or exclusion. The same is true

of the presence or absence of risk factors for serious disease. We are conducting a study to see what kind of efficacy we can confirm by having a wide range of patients and quarantined infected people take the drug.

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

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Here is a list of evaluation items and their characteristics.

Since this is an exploratory study with only 69 patients, the primary endpoint is to evaluate whether this antiviral agent can actually fulfil that role and reduce the virus.

We analyzed viral titer and viral RNA data from various perspectives and characterize antiviral effects. In addition, as we are announcing the results today, we would like to discuss the clinical significance of this antiviral efficacy in terms of clinical symptom scores, likelihood of severe disease, and other endpoints. In addition to the results of this evaluation of efficacy, finally we would like to briefly discuss the results of the safety evaluation.

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

Here is a brief summary of the background information of the 69 patients who were registered for this study.

The ITT group is defined at the bottom of page4. Each facility or testing center enrolled patients who tested positive for COVID-19 in this clinical trial. However, when we repeated COVID-19 testing using PCR, we identified some patients who tested negative. Those patients were excluded from the calculation. Therefore, we started with 47 patients for the evaluation of efficacy, and all patients who took the drug were included in the evaluation of safety.

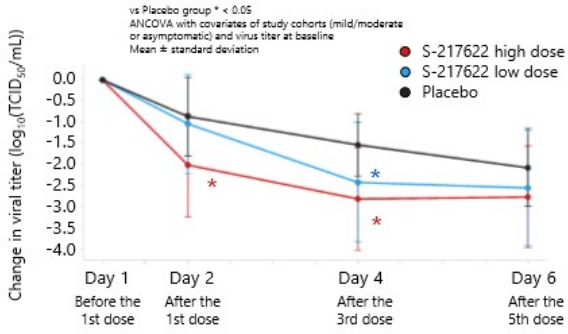
In terms of gender, male and female patients were balanced. In terms of age, as you can see here, there was an age range of patients, with both younger and older people taking the medication. The oldest patient was 63 years old. Today, I think the main key will be the efficacy of mild/moderate disease in each cohort.

We mentioned that we did not include vaccination status as an inclusion or exclusion criterion. Global competitors have examined how effective they can be in non-vaccinated patients and in patients with risk factors for severe disease. Of course, such evidence is important. However, in the current medical environment in Japan, the necessary evidence is how to quickly improve the symptoms and suppress the transmission of the virus in patients who are vaccinated and have no risk factors. With this in mind, we registered patients regardless of vaccination status.

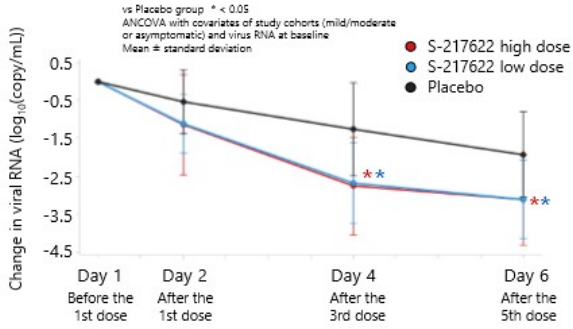
Many Japanese people have been vaccinated, so we took data under the condition that 70% or 80% of the people had been vaccinated.

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

Next, measures of effectiveness.

This is a repetition of what We mentioned the other day, but We would like to show you the results of the two tests on the left and the right, regarding the degree of antiviral effect.

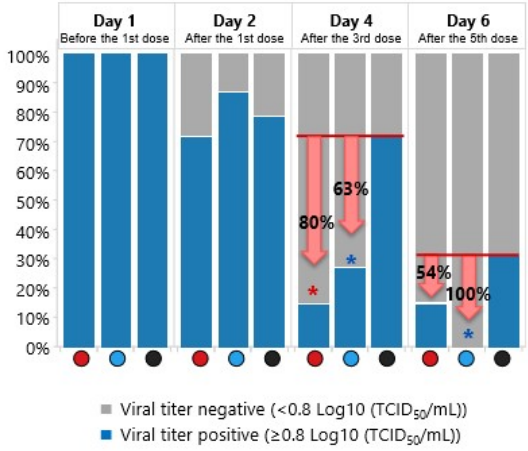
As we can see from the graph on the left, in the placebo group, infectious virus titer gradually fell over time. However, we can see that S-217622 rapidly accelerated the disappearance of the virus and stopped viral shedding.

On the right, we can see the result for amount of viral RNA. This gives an indication of viral level regardless of whether the virus is alive or dead, evaluated from copy number by PCR. As you can see, at both doses, we were able to confirm the antiviral effect compared to the placebo.

The next slide summarizes the results from the perspective of the clinical significance of such an early reduction in viral titer.

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

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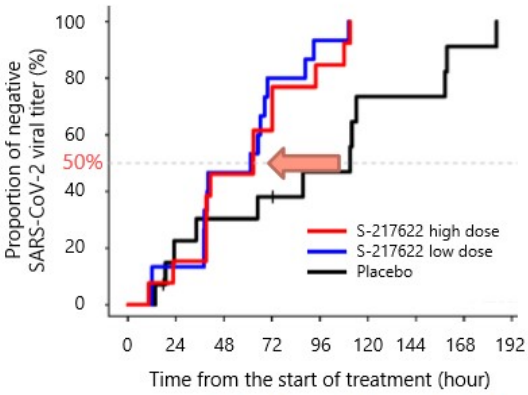
The percentage of patients with a viral titer equating to a positive is shown here. At present, people need to be isolated to avoid transmission of the virus seven days after infection. The figure was originally 10 days. If you look at the rightmost bar, the placebo arm, you can see that even at day six, the placebo group was still shedding virus.

However, more than 80% of the patients who took S-217622 were confirmed to be negative for the virus on day four, after having received three doses. We have therefore confirmed the effectiveness of this treatment in reducing the number of patients who are positive for the virus, by 63% to 80% compared to the placebo group.

We think this shows that we can expect this treatment to be effective in quickly stopping infectious virus particles from leaving the body.

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

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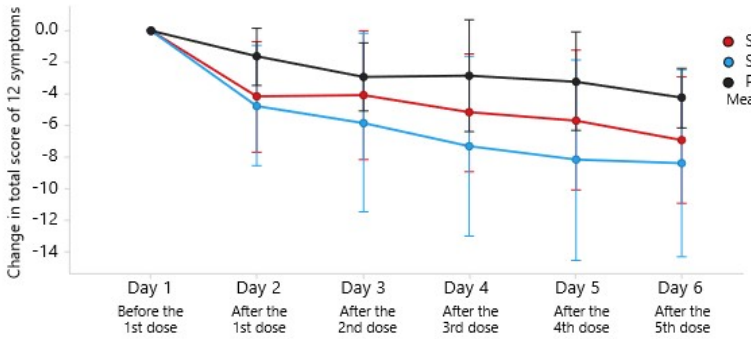
We also compared the median, placebo time to negative viral titer by Kaplan-Meier estimation. The black line is the placebo, and the blue is low dose of S-217622 and red lines is high doses of S-217622.

As you can see, both the low and high doses shorten the time for viral shedding by over two days at the median. The antiviral effect is also reflected in these figures.

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**

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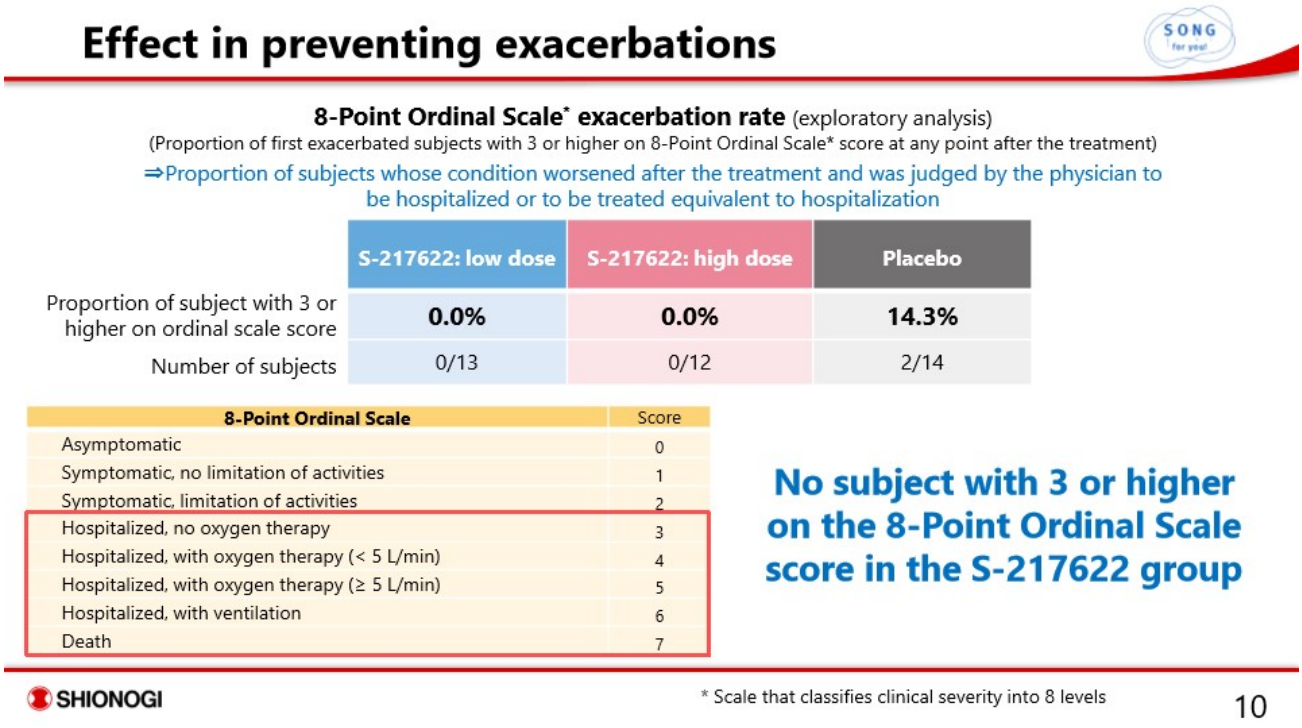
Over the next few slides, we would like to show our evaluation of how clinically significant the effectiveness of this antiviral effect is.

In this test, we graded the 12 symptoms that are said to characteristically occur in COVID-19 infection, including systemic symptoms, respiratory symptoms, and gastrointestinal symptoms. We graded these according by three levels: mild, moderate, and severe, and scored them. The cumulative score was calculated at one day pre-administration, and then we plotted how the score decreased from there in the placebo and actual drug groups.

As you can see, even with placebo, there was a gradual reduction in the score: that is, symptoms were reduced. However, with the actual drug, the reduction in score tended to be faster.

Of course, it is not data that shows a statistically significant difference because of the results of a dozen cases.. However, we believe that lowering viral titer may have a tendency to alleviate these symptoms, and that this is a promising result.



Another important factor is that people who are infected with COVID-19 and symptomatic may need to be hospitalized, need various different kinds of care, and may become exacerbation. This is very concerning.

In fact, in our trial, two of the patients who took the placebo became exacerbation. Specifically, in our study, an eight-point ordinal scale is used to define patient state at each contact with a doctor to determine the category. This scale includes factors such as whether or not in the doctor's opinion the patient's symptoms interfere with daily life, and whether the patient requires hospitalization or equivalent treatment.

Under this score, two patients in the placebo group worsened to a score of three, but none of the 25 patients who took S-217622 worsened to a score of three. This hints at the possibility that the drug may reduce the risk of serious illness.

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**

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

Lastly, we would like to talk a little bit about safety indicators.

This table shows the number of cases and incidence of adverse events and treatment-related adverse events, respectively.

As we are dealing with a COVID-19 infection, there are various adverse events that can occur. When we looked at the number of patients with adverse events in the low dose and placebo group, we found that 11 and 9 patients, roughly the same number of patients, experienced adverse events. The incidence of adverse events tended to be slightly higher in the high-dose group. we will talk about this in more detail later in the next slide, which shows a break down.

Among the adverse events and treatment-related adverse events observed, there were no severe or serious adverse events or treatment-related adverse events that could lead to discontinuation of treatment. Almost all symptoms were mild, especially those that were judged as treatment-related adverse events.

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%)

It was noted that the frequency of treatment-related adverse events was a little higher in the actual drug group, especially in the high-dose group, and here is the breakdown.

The results for the 5% or higher incidence rate are shown here.

A decrease in HDL and an increase in triglycerides have already been observed in the Phase 1 trial that we conducted. This change was observed in single-dose administration, but was a temporary change that resolved on cessation of treatment. However, there were no subjective symptoms, and no other adverse events. Therefore, we have judged that there is no problem with tolerability.

In this study, the patients who showed these changes did not have any particular treatment-related adverse events or adverse events, so although these changes were observed, we interpreted them as changes without any particular problems.

The AST and ALT test results, which could show liver damage, are shown here. As you can see, the aggregate results do not suggest that there is a risk of liver damage when compared to placebo.

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)**

Although various adverse events may occur, we have compiled a list of those that are judged by physicians to be treatment-related, in the form of adverse events for which a causal relationship with the administered specimen cannot be ruled out, or for which a causal relationship cannot be ruled out. Those with an incidence rate of at least 5% are shown here.

In the low-dose group, 5 out of 21 patients were judged to have treatment-related adverse events. Three of those had the decrease in HDL that I mentioned earlier. Two patients had abdominal discomfort on the day after administration, and there were some findings in the form of abdominal discomfort and a slight drop in neutrophils seen in one case. There was no possibility of a dose-related effect, so we do not think it is a particularly worrisome safety signal at this point.

In the high-dose group also, these changes in HDL and triglycerides were observed.

Summary

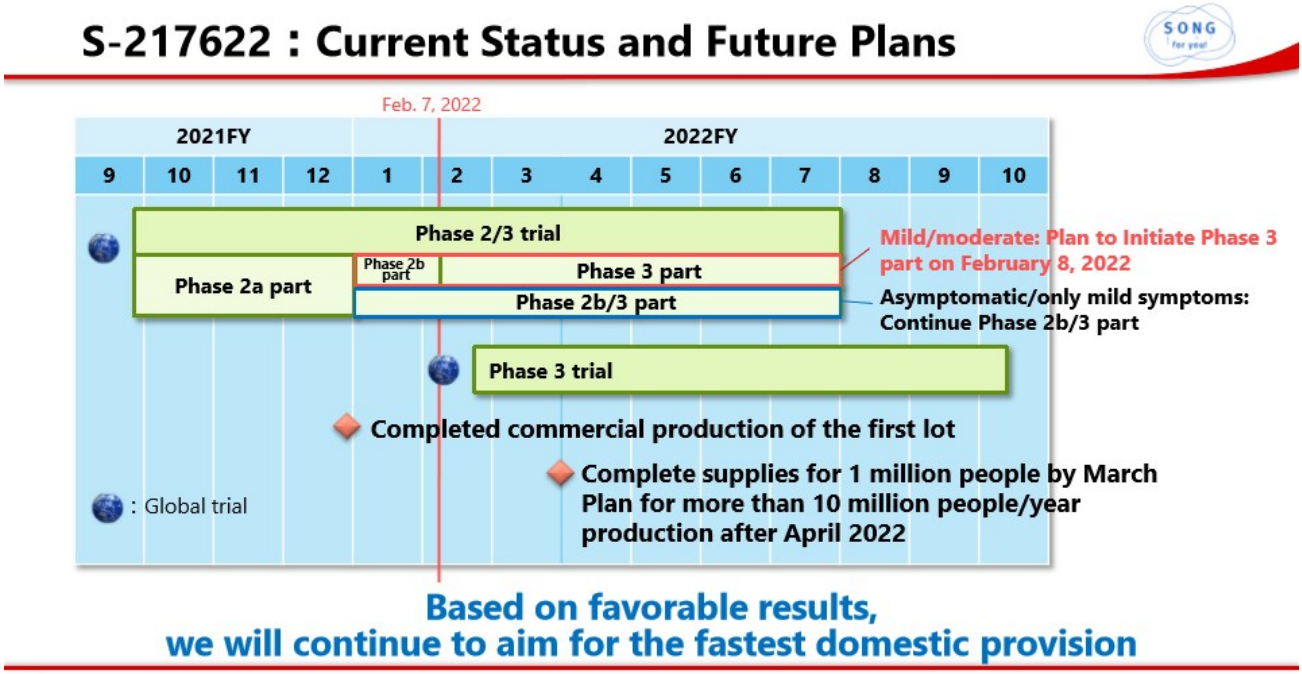
- **Antiviral effect**
  - The S-217622 arms showed a significant difference compared to the placebo group with respect to each of the following:
    - > Rapid reductions in viral titer and viral RNA
    - > On day 4, the proportion of subjects with positive viral titer decreased by approximately 60-80% 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

This is a summary of the results.

We have confirmed the antiviral effect of S-217622.

Additionally, our current results show an associated improvement trend in clinical symptoms.

In terms of safety, there have been no serious adverse events that could lead to the discontinuation of treatment. The results of the evaluation showed that the drug is well tolerated. Almost all adverse events were mild, and all treatment-related adverse events were mild.



Lastly, I would like to talk about the current status and future plans. At the beginning of the presentation, Dr. Teshirogi talked about how our drugs will be used in Japan in the future. The results I presented today were the results for the Phase 2a trial.

The original plan was to complete the accumulation of cases in this 69-patient study in a very short period of time and to move to Phase 2b/3 part immediately. However, after the Olympics, the number of COVID-19 infections decreased significantly in Japan, so it took some time to accumulate cases. We conducted the Phase 2a part of the trial over three months, and the results are now being presented to you. Additionally, we started Phase 2b part immediately after completing this case series. The original plan was to accumulate about 2,000 cases in this Phase 2b/3 part.

But rather than submitting an application for approval after the accumulation of all 2,000 cases, we would like to submit the data of about 400 cases from the Phase 2b part, in order to confirm the results as soon as possible. This would build on our confirmation of efficacy and safety trends so far. We would like to complete all Phase 2b registrations tomorrow, and based on the results, we would like to discuss whether or not approval is possible and whether or not conditional approval is possible. We have already completed commercial production of the first lot and are ready to provide the product to one million people by March.

The authorities are also carrying out GMP inspections, and we are accelerating the development of the drug in Japan so that we can deliver it to the Japanese people as soon as possible.

In parallel, we are in the midst of discussing with the US government how to proceed with the final design of the global Phase 3 trial based on the results of Phase 2a Part. As soon as those discussions are over, we plan to determine the dosage and the protocol, and proceed with the Global Phase 3 trial as soon as possible.

That is all from me. Thank you very much.

Kyokawa: Thank you very much.

Question & Answer

Kyokawa: We will now move on to the question-and-answer session.

First, Mr. Ueda of Goldman Sachs, please go ahead.

Ueda: I'm Ueda from Goldman Sachs Japan.

First, I would like to know what you think about effectiveness. In this study, there were many patients who had been vaccinated, but the vaccination rate in the placebo group was slightly lower than that of the treatment group. Similarly, the rate of worsening of clinical condition was higher in the placebo group. I think it is difficult to know whether this is the effect of the therapeutic drug or the vaccination. With this in mind, could you comment on your thoughts about the effectiveness of S-217622?

Uehara: Thank you for your question.

The rate of hospitalization and the mortality rate, exacerbations rate are reported in the news every day. The risk of exacerbations is higher in people who have not been vaccinated. In our study, these two patients, who had not been vaccinated, actually developed exacerbations.

In our study, although there was some imbalance, S-217622 was given to unvaccinated patients, and there were no cases of exacerbations in this group, even among all unvaccinated patients.

Ueda: Thank you very much.

Secondly, I would like to know your thoughts on safety. Originally, one of the characteristics of S-217622 is that it has fewer drug interactions than leading other drugs, which I think is one of its strengths. In the beginning, there were some patients who were excluded from the study, such as those who were taking CYP3A inhibitors, those with impaired liver or kidney function, or pregnant women, because there were still some unknowns. However, based on the results of the preclinical and clinical trials, I would like to know if there is any response or data that could lead to the expansion of the target population.

Uehara: Thank you for your question.

As you pointed out, drug interactions, including those for which we don't have sufficient data at this point, may cause fluctuations in blood concentration, so we basically do not allow concomitant administration.

We are now in the process of obtaining data on the clinical significance of drug interactions in combination with various drugs. Based on this data, we will be able to prepare a flowchart of who can use the drug in the future, and then we will be ready to market it.

In addition, it would not be indicated for pregnant women, even if there are no safety concerns identified. We think that the prescription of the drug will be expanded after the accumulation of evidence based on the balance of various risks and benefits. Even if S-217622 Was widely approved in this fiscal year in Japan, W

we think it would not be indicated for use in pregnant women.

We characterize the drug by accumulating safety data, and if the safety risk is less than the benefit, we make the drug available for use.

Teshirogi: Dr. Uehara probably has some difficulty in saying this, so please allow me to add a few words.

Consider the case of ritonavir, it has wide range of drug interactions. Because drug interactions of ritonavir have been investigated in its history. Although there are few examples compared to ritonavir, S-217622 also has not zero drug interactions. As for how it compares to ritonavir, since ritonavir is quite broad, we think it may be less than that, but we are now diligently investigating the extent of the difference.

Therefore, we think that none of the three drugs are completely free of drug interactions, and indeed, they are unlikely to be indicated for pregnant women, but we think that S-217622 is certainly competitive enough in these terms.

Ueda: Thank you very much. That's all from me.

Hashiguchi: My name is Hashiguchi from Daiwa Securities. Thank you.

First, I would like to ask about patient demographics. The slide shows the number of unvaccinated patients in the ITT population, but could you please disclose how many of the patients included in the analysis of effectiveness were unvaccinated?

Uehara: Thank you for your question.

Specifically, the fourth slide shows the ITT population, which is shown as vaccinated, and this population is the target population for the evaluation of efficacy.

Hashiguchi: For example, on page 10, the sample group sizes for the reduction of disease severity are low dose,13, high dose,12, and Placebo14. These numbers are a little lower than the numbers on page four. Do you have any data on how many unvaccinated patients were included in the data collected for the analysis on page 10?

Uehara: Yes. I don't have the numbers to hand, so I will have to get back to you if that's okay.

Hashiguchi: Yes, thank you.

Secondly, in the Phase 2b/3 trials, what is the difference between the Phase 2b part and the Phase 3 part? Is the former simply an early interim analysis? Are the basic target population, administration method, and evaluation items the same? Also, has a dose been identified, or will this be narrowed down in the future?

Uehara: First of all, as for the endpoint, the Phase 2b/3 part originally evaluated the disease duration, where the endpoint is time to recovery from symptoms. However, as you know, there are many vaccinated patients who recover from their symptoms very quickly. In order to show statistically significant differences in time-to-event, we need a large number of cases.

With this in mind, if an application for approval is filed only after a sufficient number of cases have been secured and the efficacy of the drug has been verified, it will inevitably take a long time. In this time, S-217622 has a confirmed antiviral effect, and we have evidence of a trend of improvement of symptom score. We are aiming for conditional approval on confirmation of these two trends, with confirmation of safety.

Under such circumstances, we would like to discuss the application for approval based on the data from Phase 2b. It is not possible at this time to answer whether the remaining part of the phase III trial should proceed with the current design, as the situation may change in the future.

Therefore, we are doing our best to collect pertinent data.

Hashiguchi: Thank you very much.

Uehara: Regarding the dosage, the main virus in Phase 2a was the Delta variant. Since January, we have been collecting cases for Phase 2b. It is likely that many of them will be the Omicron variant.

Therefore, the characteristics of the data will change, and although we have confirmed the same efficacy against the Omicron strain in non-clinical studies, we will decide on the dosage for the Phase 3 trial after making a final evaluation on which dosage is superior.

Hashiguchi: The design you have explained so far is the design for Phase 2b part, and the design for Phase 3 trial is still in flux, is that right?

Uehara: What I explained today is the design of Phase 2a part. From there, we are in the process of revising the protocol for the design of Phase 2b part. Specifically, the protocol has been revised to include antiviral efficacy as the primary endpoint and clinical endpoints as co-primary endpoints.

Hashiguchi: Thank you very much.

Sakai: This is Sakai from Credit Suisse.

I think the idea that it would be difficult to get approval with just 40 or so case was our consensus.

You mentioned that you were going to take 400 cases, from the original 2,100 of Phase 2b. How much progress has been made in registering the 2,100 patients as a whole?

Uehara: Thank you for your question.

The accumulation of the 400 cases will be completed tomorrow or the day after tomorrow, so we are preparing to start the Phase 3 trial tomorrow or the day after tomorrow.

Sakai: So, Phase 2b, which you mentioned, will be completed after 400 cases. And after that, you are going to start Phase 3.

The question is how much agreement has been reached between the PMDA, the Ministry of Health, Labour and Welfare, and the politicians on the data of these 400 cases? Has a pathway been confirmed in which if the results for these 400 patients are satisfactory, special approval would be given?

Uehara: At this point, we are discussing with the Ministry of Health, Labour and Welfare and PMDA about modifying the protocol. We have confirmed that if the excellent effectiveness data seen in Phase 2a are replicated in the data this time around, we can expect to move forward in the form of a conditional approval.

Sakai: Understood. When will the analysis of these 400 cases be finished?

Uehara: Assuming that the last patient-in is done tomorrow, we will conduct the virus test and lock the database, so we are preparing for the approval process with the results next week or the week after. We are preparing to submit the application with the results in February.

Sakai: Understood. Thank you.

Finally, a question about the drug profile. The Omicron strain in Japan is characterized by a high rate of infections between members of the same household. If this is not stopped, it will probably have a major impact on schools and other institutions. In that sense, I guess this data can be used to show that the virus titer can be reduced at an early stage and that there is a preventive effect.

Uehara: For these 400 patients, we carefully collected swabs from all the patients and processed them for measurement of the titer that we have shown you. Therefore, we have designed the system in such a way that we can evaluate the number of days that the virus was actually shed in the tests in which the majority of subjects had the Omicron strain.

However, when such data is actually available, a different design is needed to show specifically how it suppresses transmission in clinical trials. That kind of design would require several thousand cases. Therefore, we will continue to accumulate such data even after approval, including data on the public health significance of the antiviral effect from the point of view of inhibiting transmission.

Teshirogi: Our thinking is that since S-217622 is for those aged 12 and above, it is okay to use it for junior high school students and high school students. However, we really need to develop it for pediatric use. It is difficult for a company to develop a drug for pediatric use unless it is approved for adult use.

In fact, we have started to design fine granules for pediatric use, although we have not disclosed much about this. We have commenced trial design to place ourselves in a good position to start a trial, but it is difficult to proceed until after the adult population is finished.

As for prophylactic administration, as Dr. Uehara mentioned, we think we need to use a different protocol, as we did with Xofluza. Here too, it is difficult to start a separate study without approval for adults, so at this point, whether it will be for ages 12 and above or 18 and above is a matter of leveling, but at this point, we have to focus on getting approval. However, we are already prepared to develop all aspects of pediatric and preventive use as part of our plan.

Sakai: Thank you very much.

Kyokawa: One more from the audience. Now, Mr. Kohtani.

Kohtani: This is Kohtani from Nomura Securities. Thank you very much for your explanation.

I didn't have much time to look at the data, but to be honest, it is a little difficult for us to evaluate what is really working when there is such an imbalance between vaccination and non-vaccination in the placebo group.

I heard you had involved in the development of Xofluza, I think you know about the data variability. For example, these symptom data probably vary a lot, whereas the viral titer is probably highly reproducible to some extent, so if you put these together, they probably differ a lot.

Since the subjects of each arm is a dozen or so people, it is probably impossible to say that there is a statistically significant difference in symptoms. With that in mind, looking at these results, what can we say decisively? In particular, I would like to confirm whether this viral titer reduction is real or not, even if there is still a placebo imbalance. Could you explain this a bit more simply for me?

Uehara: In today's presentation, we have detailed subgroup analysis, and of course, as you mentioned, it is very difficult to interpret the data in terms of further subdivision because of the small number of subjects. However, we have analyzed the antiviral effect based on the presence or absence of vaccination.

Even when the trial was limited to patients who had been vaccinated, a clear antiviral effect was confirmed, so I think it can be said without a doubt that the antiviral effect itself was clearly confirmed regardless of whether the patients had been vaccinated or not.

However, regarding your point in term of the baseline variability, this trial is, of course, the small number of cases. The data shows the variability adjusted at baseline, but there is a clear difference even in the

unadjusted data. Therefore, it is felt as a person in charge of our company that the antiviral effect can be confirmed not only by the difference in baseline but also by the effect of the drug, and we also communicate with external doctors in this way.

We have received comments from external doctors that it is very effective, and it has a higher antiviral effect than other similar drugs.

Kohtani: By the way, is the baseline viral titer the same with or without vaccination? Does the baseline not change?

Uehara: We only have limited data on unvaccinated cases, so it is quite difficult to say. There were nine unvaccinated patients in total. So, please wait for the data next week. The data for 400 cases will be available soon, and we hope to be able to provide more robust data at that time.

Kohtani: Understood.

Also, regarding the viral titer test, is it correct to say that it's very different from the PCR cutoff that we usually see in viral RNA tests? I believe it's your company's assay.

How should we evaluate the percentage of this virus-positive patients? Could you tell us the significance of this result compared to the PCR test?

Uehara: Regarding PCR test, of course, there is the question of where to set the primers, but basically, the PCR test involves replicating a fragment of the viral genome and testing the copy number. Therefore, if a fragment of the virus is found in a cell, whether it is alive or dead, it will be detected in the sample. I think everyone is well aware of the fact that PCR positivity lasts for a relatively long time after infection.

In the US, the guideline require five days of isolation, and after that the people can go out as usual if they wear a mask. In Japan, it's seven days. The reason for this is that it is known that the risk of transmission to others is extremely high when the viral titer is high.

We included this analysis in our trial. The cell line we used is generally used as an established cell line, and is genetically modified to inhibit the factors that prevent virus attachment and infection when the virus is attached. This is the cell line that is most highly recommended by the National Institute of Infectious Diseases as a global standard, and it is used in this evaluation method to detect the sensitivity of virus infection in cells in vitro.

Therefore, we believe that we are able to evaluate infectious viruses with the current evaluation system that measures viral titer.

Kohtani: Understood.

Lastly, talking about symptoms, I believe Pfizer has conducted the EPIC-SR, a Phase 3 trial for patients with a standard risk. In this trial, there's no difference in symptom improvement in 13 days. Given that, I think that comparing the symptoms probably wouldn't make a difference. But do you really have to make this kind of test?

Uehara: There is no definite answer to the question of exactly what endpoint should be used to determine the clinical efficacy. With the shift to the Omicron variant, the severity rate has fallen significantly. In the US, the criteria for approval in the Emergency Use Authorization are to reduce the rate of serious illness and to provide study evidence. Other companies around the world are trying to obtain the evidence that reduces the risk of serious illness in people with risk factors who have not been vaccinated.

Even with the increase of Omicron variant and the decrease in the severity rate due to, I wonder if accumulating data on tens of thousands of cases is really necessary for emergency approval. This drug, like all drugs, has an antiviral effect that reduces the viral titer. Under such circumstances, we will of course be conducting Phase 3 trials, which we are discussing with the FDA, in pursuit of such figures.

The regulatory authorities have said that in addition to verifying the antiviral effect, some kind of symptom improvement effect is also required for approval. Therefore, we are currently designing a plan to proceed with the application for approval after verifying the antiviral effect and the improvement in clinical symptoms.

Kohtani: Thank you very much.

Kyokawa: Now I would like to move on to questions from web participants.

Operator: If anyone has any questions, please raise your hand.

Now for the first question. Mr. Yamaguchi, Citigroup Securities, please go ahead.

Yamaguchi: Thank you very much. I have three short questions.

In the chart on page 9, the dose-response graph seems to be upside down. As you mentioned earlier, this may be due to the fact that symptom status is difficult to measure. In particular, the high-dose drug group seems to level off. Could you give us your opinion?

Uehara: Thank you for your question.

Since the results of the analysis were based on a very small number of cases, variations in the baseline and data at each time point are inevitable.

In this context, there were also three cases of headache in the high-dose group. If such adverse events were to occur, the score might fluctuate, so we are analyzing the data from various perspectives.

Yamaguchi: Thank you very much.

Also, you explained about the endpoint of Phase 2b. Is it possible to use almost the same result as that of Phase 2a that you showed us today? There were several types of antiviral effects, so I was wondering which would be used in Phase 2b.

Uehara: Specifically, in terms of antiviral effect, we are planning to verify the superiority of the viral titer change over placebo, as well as how to reduce the symptom score, as I have indicated.

Yamaguchi: Thank you very much. So, would that be the left-hand chart from page 6?

Uehara: Yes, that's right.

Yamaguchi: So, you're going to look at two things: the viral titer, as in the left side of slide 6, and the symptoms as mentioned earlier.

Uehara: That's right.

Yamaguchi: Understood.

Lastly, could you comment on the timeline for the start of Phase 3 in the US? It is able to start today. I might be getting mixed up.

Uehara: I'll go over it again. Please take a look at page 16.

In the upper row are the Phase 2/3 trials that are currently being conducted mainly in Japan. The one starting tomorrow is the one surrounded by this red box, which is being conducted mainly in Japan. We have completed the accumulation of over 400 cases for Phase 2b, so we are moving directly to Phase 3.

On the other hand, the global trials centered in the US are shown below as Phase 3 trials. Specifically, we are in the process of finalizing the protocol design with the FDA based on the results of the Phase 2a POC that I showed you today.

There has been a great deal of discussion about what the dosage should be and what kind of study design should be used to approve future drugs in the US. In the meantime, once the protocol and dosage are agreed upon, we plan to start Phase 3 trials globally at the end of this month.

Yamaguchi: Thank you very much.

Operator: Moving on to the next question. Ms. Kumagai of Mitsubishi UFJ Morgan Stanley Securities, please go ahead.

Kumagai: I'm Kumagai from Mitsubishi UFJ Morgan Stanley. I have one question.

I'd like to ask about the decrease in HDL and increase in triglycerides noted in the side effects section. This seems to be occurring at a rather high frequency, especially at the higher doses, so I wonder if you could tell us what kind of impact this will have on the doses used in Phase 3 in Japan or overseas.

Related to this, this slide shows that safety and recoverability of these events has been confirmed in doses of up to 2,000 mg. I don't know exactly how many mg is the high dose that is being used now, so I would appreciate if you could give us a hint as to how far it deviates from this 2,000-mg figure.

That's all. Thank you.

Uehara: Thank you for your question.

The decrease in HDL is clearly dose-dependent, as described here for Phase 1, and such changes have been observed even with single-dose administration. Therefore, as a characteristic of this drug, it has been confirmed that it slightly modifies the lipid balance, but there have been no subjective symptoms, adverse events, or other events based on this change.

This has been observed in animal studies. In these studies, even when the dose was raised to a level where extreme toxicity was observed, there were no toxic changes associated with a decrease in HDL. Therefore, we do not consider it to be a risk so far.

As for the dosage, it is not disclosed at this time. We have confirmed safety in a dose as high as 2,000 mg.

Teshirogi: I'd just like to disclose that even at the high dose used in this trial, it is still only about a third of that 2,000-mg level.

Kumagai: Understood. Thank you very much.

Operator: Moving on to the next question. JPMorgan Securities Japan, Mr. Wakao, please go ahead.

Wakao: I'm Wakao from JP Morgan. Thank you.

This time, I think the primary endpoint was to see the trend of symptom improvement. Is it correct to say that if there is a statistically significant difference, it is a success? My first question is whether that is correct, and over how many days have you seen this trend?

Uehara: At the moment, we are communicating with the PMDA, and we are designing a trial that can show a statistically significant difference in the change in symptoms by day 6, after the completion of 5 days of treatment. The number of patients in each group should exceed 100.

Wakao: I understand.

Also, I think the endpoint was changed this time due to the fact that the Omicron variant is now prevalent. I think that symptomatic improvement will take place faster with the Omicron variant. Does your trial factor that in? I think your company is confident about the improvement of symptoms, but I wonder if you could tell us your current thoughts on the probability of success. That's my second question.

Uehara: Thank you for your question.

We believe that the Phase 2a trial was mostly testing patients with Delta variant. Since the beginning of the year, we started accumulation of Phase 2b data, and the Delta variant has been almost completely replaced by the Omicron variant. So indeed, the type of virus being tested is different.

The most common symptoms of Omicron variant are sore throat, fever, coughing, and less frequent taste disorders. We did not select symptoms specific to the Omicron variant, but rather based on the 12 representative COVID symptoms, so I think that no one can be sure whether we can get significant differences by scoring these symptoms.

With that in mind, we will accumulate various data to see the effectiveness. However, considering the fact that such symptoms are caused by the presence of the virus, if the viral load is lowered, we are confident the symptoms will improve.

Wakao: Thank you very much.

Is the trial designed in such a way that all symptoms need demonstrate effectiveness? For example, if you only demonstrate effectiveness of 9-symptoms instead of 12, can you still evaluate the effectiveness of the drug?

Uehara: As I'm sure you already know, the goal is to show a significant difference in a predetermined endpoint, which is the domain of statistical validation, so you have to choose one.

In this case, we have selected this 12-symptom scale. However, if we can read the data in a biologically meaningful way in spite of there being no significant difference using the 12-symptom scale, or if we can look at individual symptoms in a way that shows that there is a clear effect in the presence of variability, then we can expect a degree of effectiveness. If we can read the data in a biologically meaningful way, we would like to communicate with doctors, regulators, and others to see if, taking the data in its totality, we can demonstrate the effectiveness of this drug.

Wakao: Understood.

I'm sorry, but I'd like to ask a third question. This drug clearly has very good antiviral activity. Overseas, the market is larger and there are more patients, so I think it is very important to deliver the product to overseas markets as quickly as possible. From that perspective, overseas partners who can take charge of manufacturing are also very important.

You are about to start Phase 3. When do you think you should decide on the partnering? You could say that you already have enough data now, and could move forward with finding a partner, or you may feel that more data would be valuable in negotiations. In any case, what would be the deadline for finding a partner? That's my last question. Thank you.

Teshirogi: I will take this question.

The current target is the end of February, but that may be extended to the first week of March.

With the data coming out so far, and the fact that we will be able to see in the next few months whether the COVID-19 pandemic will end with Omicron variant or whether new variants will develop, it will be important for global companies to start Phase 3 in February or March.

Wakao: Thank you very much. Understood.

Kyokawa: We are out of time, so I would now like to conclude today's briefing.

Thank you all very much for taking time out of your busy schedules to participate.

Teshirogi: Thank you very much.

[END]