SHIONOGI & CO., LTD.

CROI 2023 Follow-up Meeting

February 22, 2023

Presentation

Kyokawa: Good morning. My name is Kyokawa, Director of Public Relations with SHIONOGI & CO., LTD. Thank you very much for joining us today. I would like to begin the CROI 2023 Follow-up Meeting.

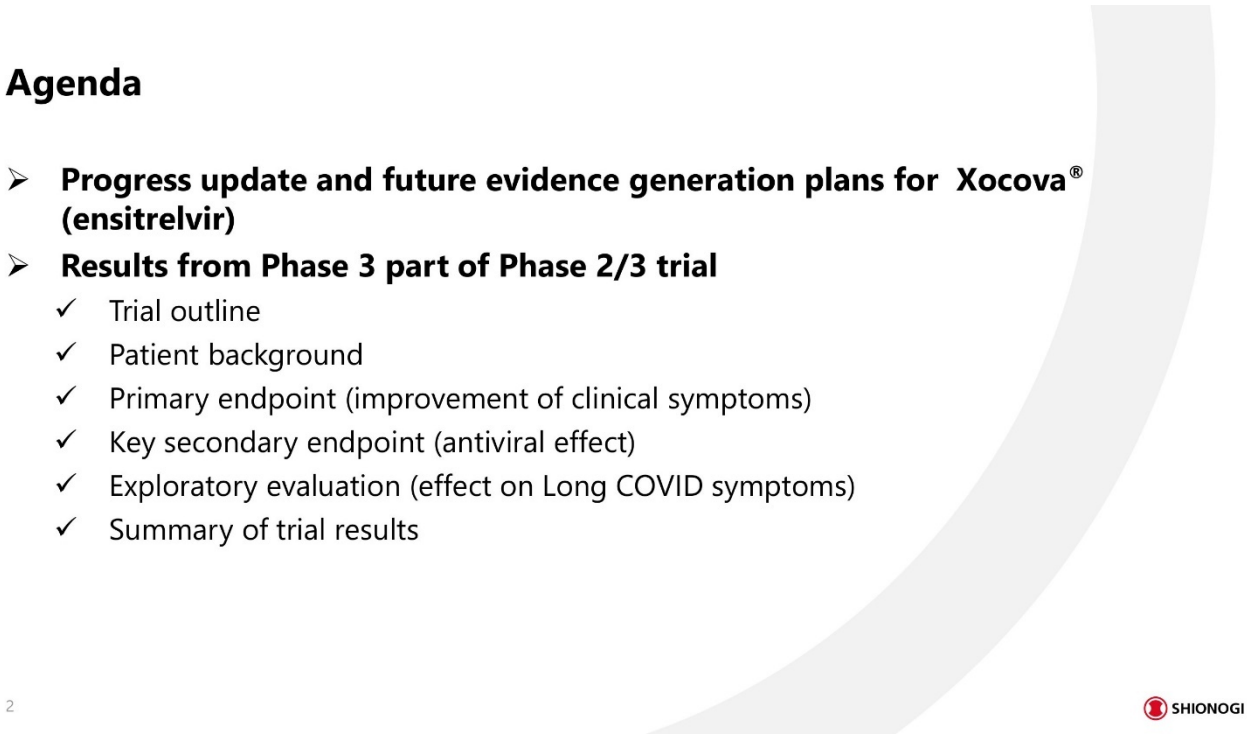
I would like to introduce today's speakers. Dr. John Keller, Senior Executive Officer, Senior Vice President, R&D Unit.

Mr. Takeki Uehara, Corporate Officer, Senior Vice President, Drug Development and Regulatory Science Division.

Mr. Uehara is joining us from Seattle. Thank you.

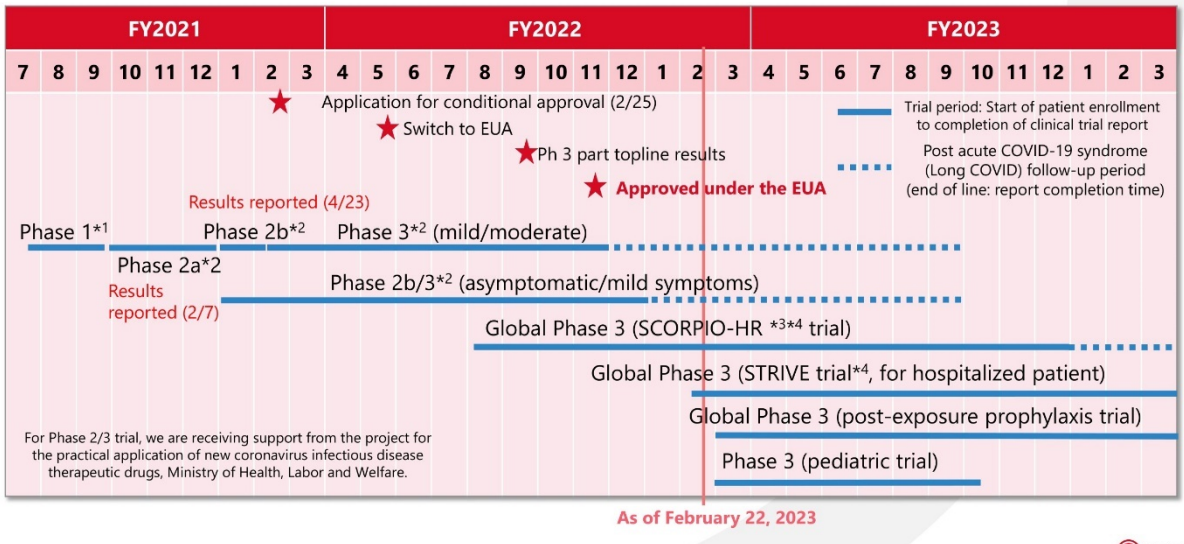
Mr. Uehara will provide an overview of the presentation he conducted for CROI. After that, we will welcome questions from the participants. This meeting is scheduled to adjourn by 9 AM.

At this time I would like to welcome Mr. Uehara.



Uehara: I would like to start by giving you a brief overview of the progress of the development of Xocova and the accumulation of evidence. Additionally, I would like to give you an overview of the results of Phase 3 part of the Phase 2/3 trial, which I presented at CROI in Seattle, USA.

Xocova®: Progress Summary



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*1 jRCT2031210202、*2 jRCT2031210350、*3 NCT05305547、*4 NCT05605093

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I have used this progress summary on various occasions. As an update since 3rd Quarter of Fiscal 2022 Financial Results Conference Call, the global Phase 3, STRIVE study has successfully achieved First Patient Enrollment and is now officially open for registration.

We are also in the process of brushing up the final version of the protocol in order to smoothly start the post-exposure prophylaxis trial and the pediatric trial.

Latest Update

- **JP: From May 8, 2023, the position of COVID-19 under the Infectious Diseases Act will be changed to Category 5 infectious disease**
- **US: Proclamation on Declaring a National Emergency Concerning COVID-19 Outbreak will be lifted on May 11, 2023**
  - Emergency use authorizations (EUA) for all antibody drugs against COVID-19 have been revoked due to their reduced efficacy against Omicron strains
- **Xocova®: Started global Phase 3 study STRIVE (announced on February 15, 2023)**
  - STRIVE is a new international clinical research program derived from ACTIV, a public-private partnership program led by the National Institute of Allergy and Infectious Diseases (NIAID), a constituent organization of the National Institutes of Health (NIH). The program is funded by NIAID
  - 1,500 inpatients to be enrolled globally, expected to be completed in early 2024

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Most recent update.

First, as you are all aware, Japan is expected to change the legal status of novel coronavirus infectious diseases from the current category two to category five, effective May 8. Also the US are circulating that the declaration of national emergency may be lifted on May 11.

One of our concerns is that many monoclonal antibody drugs, or neutralizing antibody drugs, have been used in the past. However, as the spike protein has been changing multiple times, the effectiveness against the Omicron subtype, which is now prevalent, has been declining, and all antibody drugs that can be used under emergency use have been withdrawn.

In this context, we are conducting the STRIVE study in such a way that Xocova may be administered even for severely ill patients. In collaboration with the NIH and under STRIVE, a platform study with NIAID, we aim to enroll 1,500 patients worldwide and have started an activity to confirm the therapeutic effect of the drug even in critically ill hospitalized patients.

Under such circumstances, we feel that there is a great unmet need for drugs with new mechanisms of action that show antiviral effects in oral formulations for use in a variety of patients.

Xocova®: Antiviral Effect Against Mutant Strains*

From the 3rd Quarter of Fiscal 2022 Financial Results (Partially revised)

In vitro antiviral evaluation using VeroE6T cells*

virus strain	Ancestor	alpha strain	beta strain	gamma strain	delta strain	omicron strain								
						BA.1	BA.1.1	BA.2	BA.2.75	BA.4	BA.5	BQ.1.1	XBB.1	XE
EC_{50} (μM)	0.37	0.46	0.40	0.50	0.41	0.29	0.36	0.52	0.30	0.22	0.40	0.48	0.33	0.44

- **Xocova® shows antiviral efficacy against a wide range of strains, including past prevalent strains and recent Omicron mutant strains (BQ.1.1, XBB.1).**
- **Xocova® has also been reported to exhibit in vitro activity against the Omicron mutant XBB.1.5****
- **Xocova® shows antiviral efficacy against viruses resistant to other drugs (no cross-resistance)**

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* Nakashima et al OPTIONS-XI P-205 Sep 2022, Sho Kawashima et al Biochemical and Biophysical Research Communications 645 (2023) P.132-136

** Antiviral and bivalent vaccine efficacy against an omicron XBB.1.5 isolate - The Lancet Infectious Diseases

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Please look at the second bullet point from the bottom.

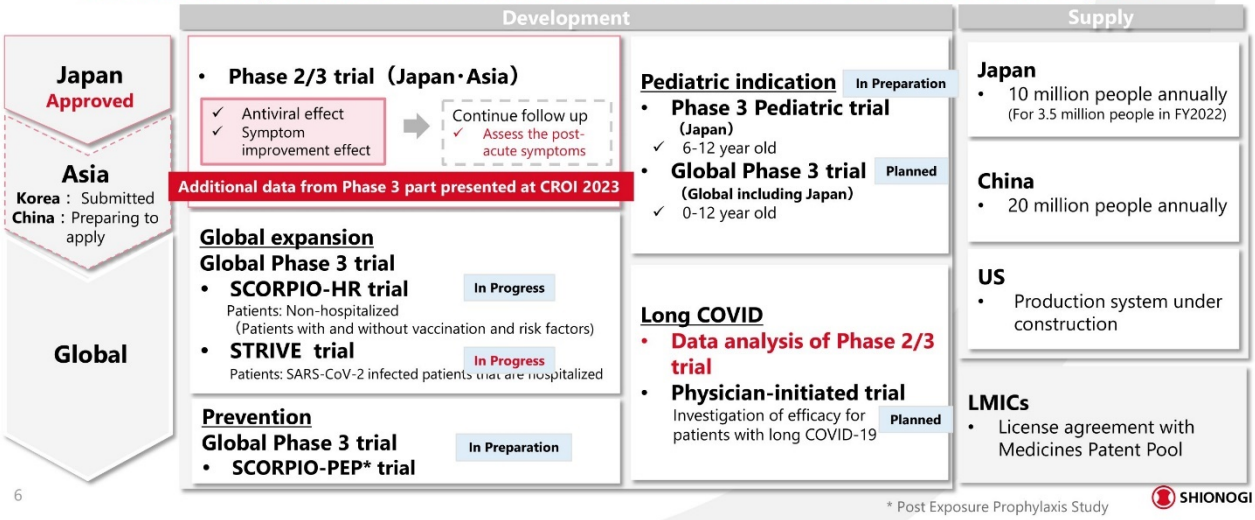
Xocova shows activity in vitro against the Omicron mutant strain XBB1.5, which is now a widespread strain, here a circulating strain. A very recent thesis in the Lancet Infectious Disease contains data from experiments conducted at Dr. Kawaoka's laboratory.

We have not yet confirmed this, but Dr. Kawaoka's lab reported that ensitrelvir is active against XBB.1.5. So, we are able to confirm that it is still an antiviral drug that can be used.

Xocova®: Overall Picture of the Current Situation and Future Plans

From the 3rd Quarter of Fiscal 2022 Financial Results (Partially revised)

With the emergence of new mutant strains, the need for antiviral drugs remains
Accumulating further evidence for the role of Xocova® in "with COVID" phase



While society is gradually returning from the state of emergency to normalcy, we believe that the role expected of antiviral agents will gradually change.

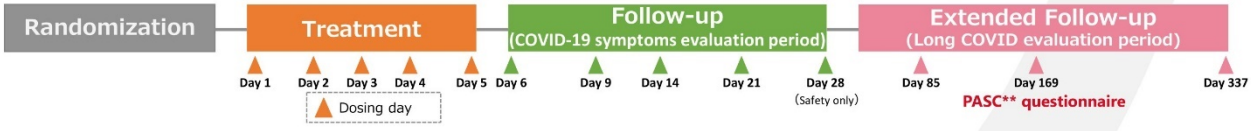
In the Phase 2/3 trial in Asia, most people are vaccinated in the real world. It exhibits antiviral effects and improve symptoms when administered to patients infected with the Omicron strain.

We were also planning to continue the follow-up evaluation of Long COVID to track after-effects.

I compiled the interim results and the data and presented them today at the CROI.

Phase 3 part of Phase 2/3 trial Outline

- **Trial purpose**
  - ➢ To evaluate the efficacy and safety of ensitrelvir once-daily, 5 days oral treatment in patients with mild/moderate SARS-CoV-2 infection, aged 12-69 years regardless of SARS-CoV-2 vaccination, and risk factors for severe disease
- **Trial design**
  - ➢ Multicenter, randomized, double-blinded, placebo-controlled study conducted in Japan, South Korea and Vietnam from February to November in 2022, Omicron variant dominant period



- **Main evaluation items**
  - ➢ Primary endpoint：Time to resolution* of five key Covid-19 symptoms
  - ➢ Key secondary endpoint：antiviral effect（viral RNA amount、virus titer）
    - ✓ Viral titer: Amount of infectious virus (living virus) contained in the sample
    - ✓ Viral RNA: Amount of viral RNA (including fragments of the dead virus genome) contained in the sample
  - ➢ Safety（Until the Day 28）
  - ➢ Exploratory endpoint: Presence of Long COVID symptoms evaluated by PASC questionnaire (by Day 169)

* Time to return to pre symptomatic state, defined as time to "recovery" in the trial protocol ** post-acute sequelae of SARS-CoV-2

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From this point on, I am sharing a slightly modified version of the presentation material I used for CROI.

For your reference, you will have access to this presentation deck, as well as the English version used in the conference, so please feel free to refer to both versions in our website as needed.

This is an examination outline for the Phase 3 part of the Phase 2/3 trial.

We have evaluated the efficacy and safety of the product in patients enrolled with or without risk factors, with or without vaccination, and after five days of administration.

Follow-up evaluation of COVID-19 symptoms continues until Day 21, which is after the treatment phase, and safety will be evaluated until Day 28. The duration of follow-up for very standard acute infections. I'm highlighting it in pink this time. We had planned in the protocol to extend the exploratory period to Day 85, three months, and Day 169. We are waiting for the six-month point, and another one year later at 337, but it has not yet been a year, so we do not have the data yet.

Therefore, the data presented here are the data up to Day 169, which is the middle of the day. In this study, we have evaluated the primary, key secondary, antiviral efficacy, and safety as the main endpoints, and finally, the risk of developing Long COVID as its exploratory evaluation.

Summary Patient Background

※The trial results only include the domestically approved dose of 125 mg of ensitrelvir. (See Appendix for results at 250 mg)

Background information on the ITT* population

	Time from onset to randomization : <72 hours		Time from onset to randomization : <120 hours	
	125 mg N = 347	**Placebo** N = 343	**125 mg** N = 603	**Placebo** N = 600
Sex, Male (%)	55.6%	50.7%	52.7%	51.8%
Mean age (years)	35.7	34.7	35.9	35.3
Vaccination for SARS-Cov-2	92.8%	91.8%	93.2%	92.2%
Viral RNA amount (log_{10} copies/mL)	6.976	6.933	6.825	6.770
Race: Asian (%)	99.4%	99.4%	99.7%	99.7%
Omicron strain infection rate (%)	89.6%	88.0%	89.7%	89.0%

* Intention-to-treat (ITT) : All subjects who were randomly assigned to the trial intervention and had a SARS-Cov-2 infection based on RT-PCR. 1,798 subjects excluding 23 subjects that were PCR negative at baseline (from 1,821 subjects)

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Because our clinical trial is independent of vaccination, more than 90% of them are vaccinated, as shown in the red highlighted fonts in the middle.

Since the majority of the study was conducted on Asians, we spike-sequenced the viruses collected from all patients. The results are complete, and approximately 90% of the patients were infected with Omicron.

The remaining 10% is not measurable.

Omicrons change in various ways, and some are hybrids, so the results are not clearly defined. However, since the registrations were made between February and July of last year, we believe that all of them are basically Omicrons. Most of the infected patients had BA.1, BA.2, BA.4, BA.5, or even higher.

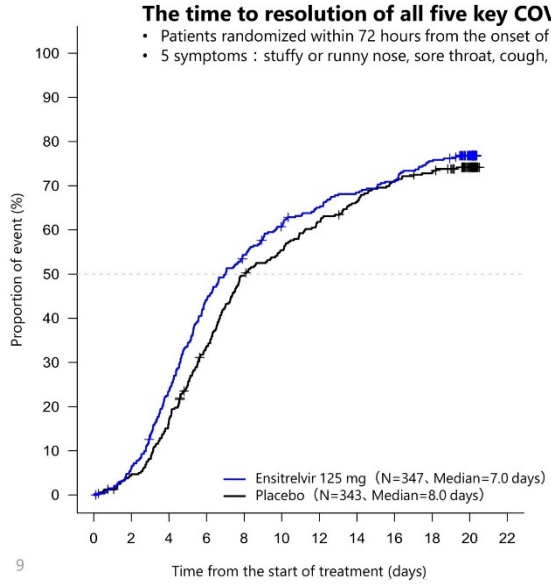
Although I presented all of the data for both the high and low doses at CROI, I would like to present excerpts of the data for the low dose, which is the urgently approved dose in Japan.

Primary endpoint: The Time to Resolution of All Five Key COVID-19 Symptoms

From the FY2022 R&D Day (Partially revised)

The time to resolution of all five key COVID-19 symptoms

- Patients randomized within 72 hours from the onset of symptoms
- 5 symptoms：stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness



Time from onset to randomization：<72 hours

		125 mg N = 347	Placebo N = 343
Median [95% CI]		167.9 [145.0, 197.6]	192.2 [174.5, 238.3]
Difference in median vs. placebo [95% CI]		**-24.3** [-78.7, 11.7]	---
Stratified Peto-Prentice's generalized Wilcoxon test vs. placebo [a]	P value	**0.0407**	---

CI = Confidence Interval
[a] Adjusted by the following stratum (SARS-CoV-2 vaccination history [Yes or No])

Significant reduction in the time to resolution of 5 symptoms of COVID-19 characteristic of Omicron strain compared to placebo (primary endpoint achieved)

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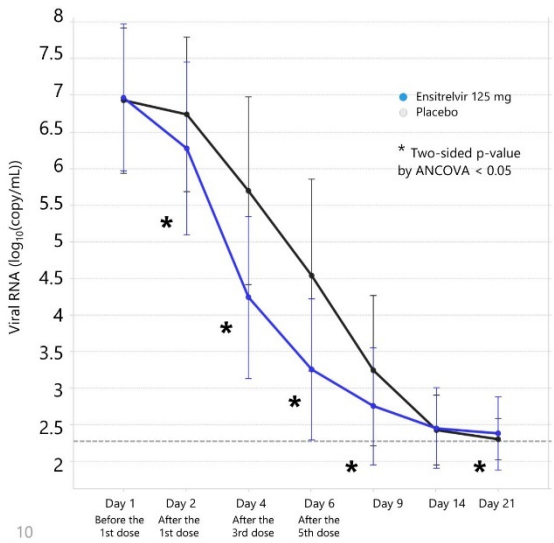
These are the results of the main evaluation.

Again, regarding the length of time that the five symptoms subside, the results showed that it took eight days when a placebo is used, and it took seven days when the drug is administered. Prompt recovery of symptoms was observed.

Key Secondary Endpoint①: Change in Viral RNA Amount

From the FY2022 R&D Day (Partially revised)

Amount of viral RNA



Changes in viral RNA levels on day 4 of administration (after 3 doses)

Time from onset to randomization：<72 hours

		125 mg N = 347	Placebo N = 343
Mean (SD)		-2.737 (1.085)	-1.235 (1.528)
ANCOVA vs. placebo [a]	LS mean (SE)	-2.48 (0.08)	-1.01 (0.08)
	Difference in LS mean (SE) [95% CI]	**-1.47 (0.08)** [-1.63, -1.31]	---
	P value	**<0.0001**	---

UNIT: log_{10} copies/mL
ANCOVA = Analysis of Covariance; SD = Standard Deviation; SE = Standard Error; LS = Least Squares; CI = Confidence Interval
Lower limit of quantification of viral RNA is 2.08 log_{10} copies/mL.
If viral RNA is negative and less than the lower limit of quantification, the viral RNA was imputed 2.27 and 2.08 log_{10} copies/mL, respectively.
[a] Covariate: SARS-CoV-2 viral RNA at baseline, SARS-CoV-2 vaccination history [Yes or No]

Ensitrelvir 125 mg group reduced viral RNA level to 1/300 of the level before administration by day 4 of administration (after the 3rd dose) (placebo decreased to 1/10)

Significantly reduced viral RNA levels on day 4 of administration (after 3 doses), confirming antiviral efficacy

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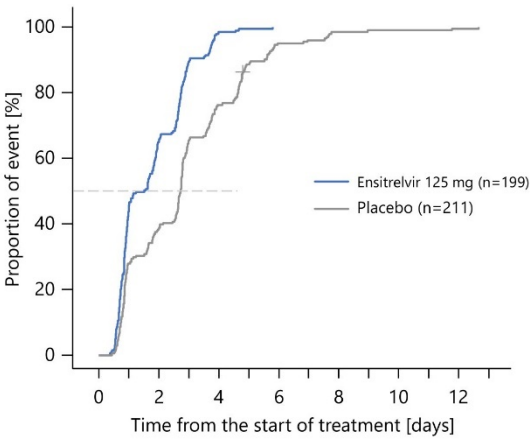
This is viral RNA. This is also the copy number of the genome of the virus measured by PCR, which we have already published. In general, PCR is very sensitive, and because it is PCR, even fragments of dead viral genomes can be amplified and captured.

In terms of evaluating the actual infection status and the amount of active live virus in the body, it is very important to use an evaluation method such as taking swabs and culturing the swabs to evaluate the amount of live virus rather than the amount of change in the amount of viral RNA. This method is also very important.

This PCR method is widely used for other agents as well, so we measured the results in our test and found that this 1.47 log reduction, or 1/30th, was achieved, so I think the data here can be seen indirectly with other agents.

Key Secondary Endpoint②: Virus Titer

Time to first confirmed negative virus titer for SARS-CoV-2



		125 mg N = 203	Placebo N = 214
Median [95% CI]		36.2 [23.4, 43.2]	65.3 [62.0, 66.8]
Difference in median vs. placebo [95% CI]		-29.1 [-42.3, -21.1]	---
Stratified log-rank test [a]	P value	<0.0001	---

Analysis in the Modified Intention-to-Treat Population (All Pretreatment RT-PCR-Positive Patients with Detectable SARS-CoV-2 Viral Titers at Baseline), CI = Confidence Interval
[a] Adjusted for SARS-CoV-2 vaccination status
Viral titer negative (<0.75 $\log_{10}$ ($TCID_{50}$/mL)) Viral titer positive (≥0.75 $\log_{10}$ ($TCID_{50}$/mL))

Ensitrelvir 125 mg significantly reduced time to viral titer negative compared to placebo

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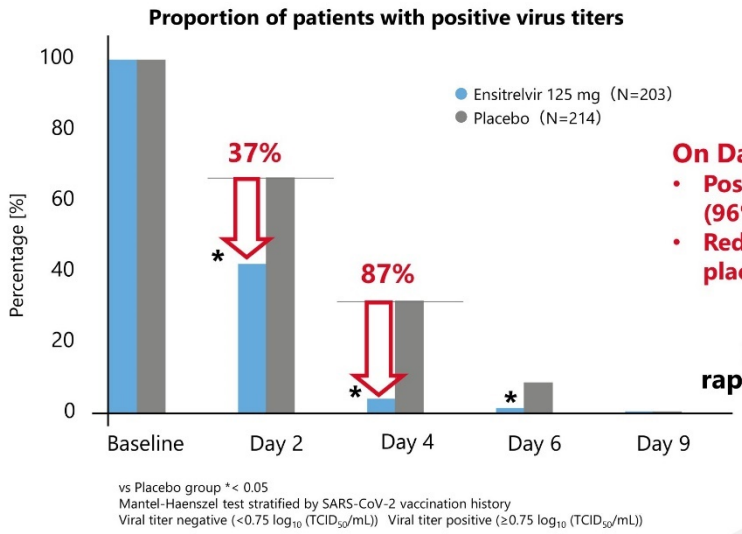
This is the new content we have told you about, and it is the viral titer.

We used the swabs to obtain the virus from inside the nose, and cultured and measured the live viral titer.

As expected, we were able to confirm in patients treated with ensitrelvir that it eliminates viruses quickly and stops viruses with infectious particles quickly.

Key Secondary Endpoint②: Virus Titer



On Day 4 (after 3 doses)

- **Positive viral titers have almost disappeared (96% negative)**
- **Reduced by about 90% compared to the placebo group**

Proportion of patients with the potential to shed infectious virus rapidly decrease after taking ensitrelvir

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As to the significance of the data, we evaluated the data in the same way in Phase 2b.

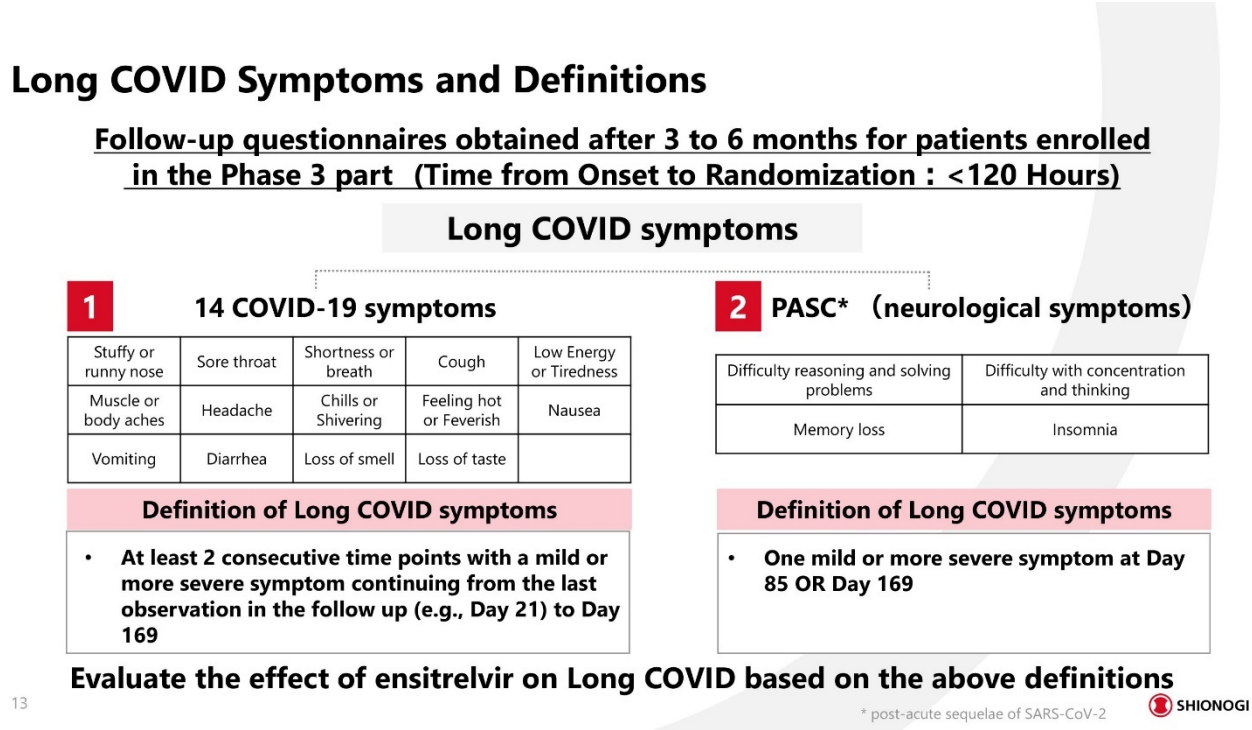
This bar graph plots the percentage of patients who had a positive viral titer at each time point. The question is: when the baseline is set at 100%, how far will it go down from there? Obviously, titers will also decrease in patients who do not take their medication after placebo administration.

However, the fact that the virus can spread and infect others very quickly makes it very difficult to control. In fact, many patients were still positive on Day2 , the day after receiving the medication, and on Day4, after three doses, about 30% to 40% of patients were still shedding the virus.

However, the results of the study showed that the drug, statistically significantly reduced the number of patients who tested positive for the virus by 87% compared to the placebo.

Incidentally, as shown in the blue bar, 96% of all cases were negative, and only 4% were positive for the virus.

We believe that the checker means that after three doses, the next day, no more live virus is detected in most patients.



Based on these antiviral efficacy data, we were also able to further analyze the Long COVID data. For Long COVID symptoms, we have obtained data in these two categories.

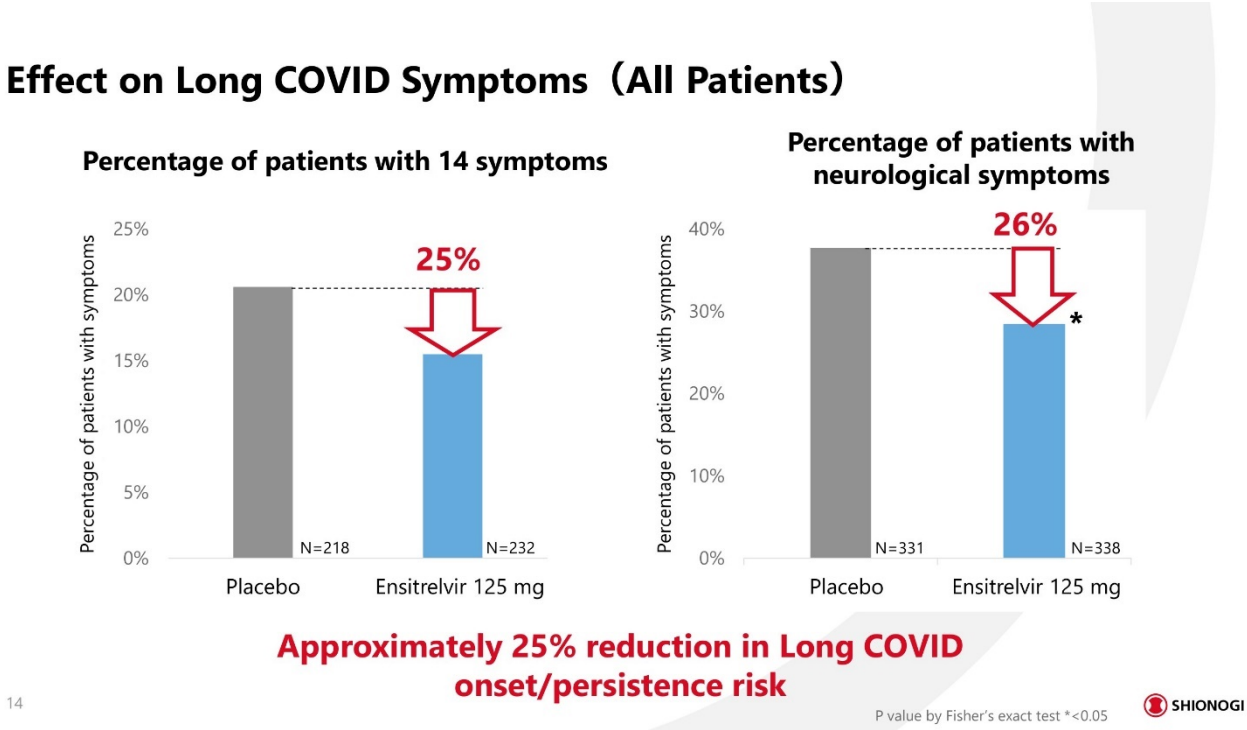
The first one, which is characteristic of COVID-19, has 14 symptoms. That is, 12 symptoms and loss of smell and loss of taste. A very common complaint is a sore throat. Some patients reported a cough that would not go away. I also heard many patients complain of low energy or tiredness.

These characteristic COVID-19 symptoms are seen from the onset of the disease, and after repeated dosing, are still present at Day 21, the end of observation, where they remain at three months and six months of follow-up.

We evaluated Long COVID from two points. The first point comes on Day 21. The second point is set at a later date. If patients experience some type of symptoms consecutively more than twice -- for example, someone with a persistent cough, or fatigue, and so on -- the first method of evaluation was to count the number of those patients.

The second is neurological symptoms often reported as a post-acute sequelae of SARS-CoV-2 symptom. It is a symptom that is not often mentioned at the time of COVID-19 onset. This is a brain fog that continues even after COVID-19 symptoms have disappeared. Some patients feel that their problem-solving ability has decreased. Or they can't concentrate things like they used to. Or they become memory loss. Also, some patients may present with neurological symptoms such as insomnia. Therefore, we were able to acquire these data as well.

Since these symptoms do not occur beforehand, they are counted at the time of follow-up, either at three months or six months, when symptoms are confirmed to be more than mild.

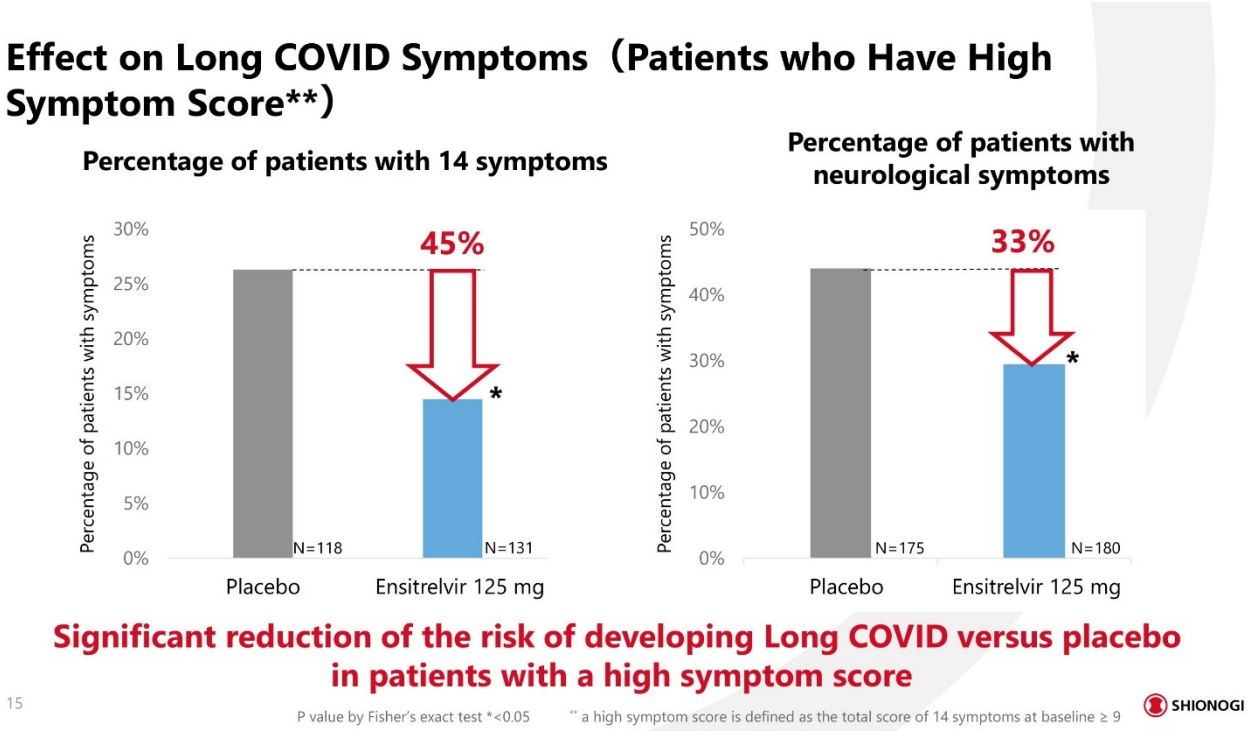


This is the result.

In terms of the effect on the risk of occurrence, the left shows the results for the 14 symptoms of COVID-19, and the right shows the results for the four neurological symptoms mentioned earlier.

Compared to the placebo, the results show a 25% relative risk reduction on the left figure, and a 26% relative risk reduction on the right figure.

Although this study was not conducted for the purpose of verifying from a statistical point of view, the results showed that there were statistically significant differences in four neurological symptoms.

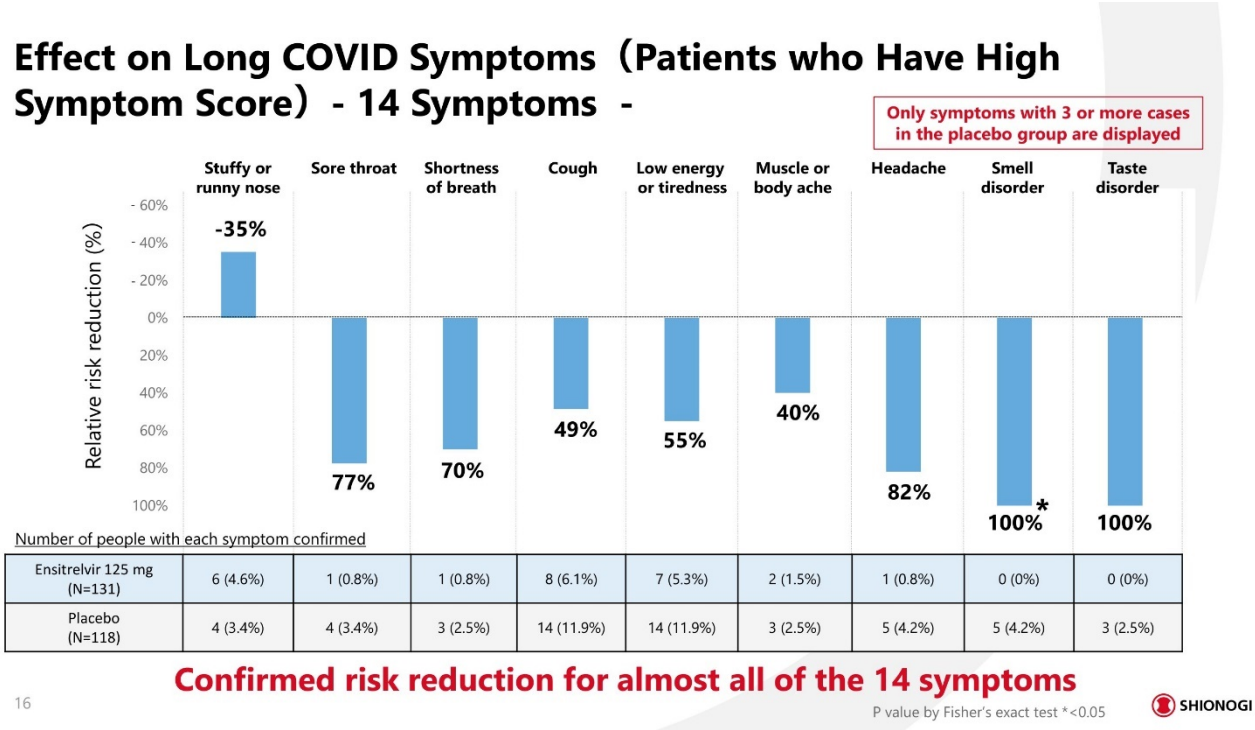


We have conducted an additional analysis. This is because many epidemiological reports indicate that patients are more likely to develop Long COVID if their symptoms are severe at the time of onset of the disease, especially if they have been hospitalized for the disease.

In our study, the patients who basically did not require hospitalization were included, but the relative risk reduction rate was larger for those with relatively high symptom scores, specifically for those with a total score of 14 symptoms above half the median.

The relative risk reduction rate is larger for patients with relatively high symptom scores. Such risk is increased for a placebo while those who were medicated with symptoms presented fewer risks.

We have confirmed a statistically significant difference.



I have shown the summary of the comprehensive total. Here is the result of the breakdown.

We have surveyed all 14 symptoms, and only the patients with three or more symptoms are shown here, because there is not much value to study those with fewer symptoms in the placebo group.

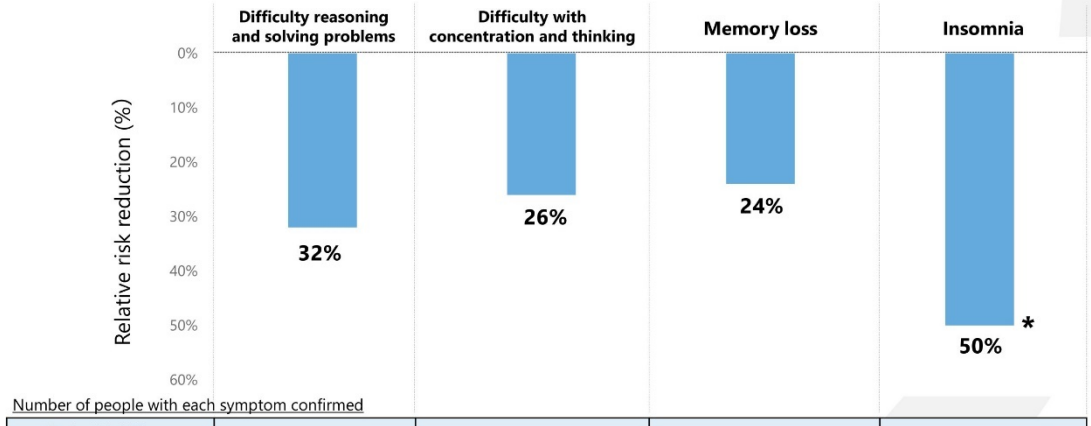
Looking at the overall results, we can see that there is a trend toward less persistent symptoms such as cough, low energy or tiredness, muscle or body ache, and other symptoms often mentioned in Long COVID, as well as smell and taste disorder, among those who received clean medications.

The results of this study suggest that the overall trend is that there are fewer patients with such symptoms who continue to develop them later in life.

Incidentally, I am not sure why only stuffy or runny nose was included, but I looked at the contents of the data and found that many of these people have hay fever, so perhaps such background information was included in the results.

In any case, I hope you can see the overall results.

Effect on Long COVID Symptoms（Patients who Have High Symptom Score）- Neurological Symptoms -



Number of people with each symptom confirmed

Ensitrelvir 125 mg (N=180)	19（10.6%）	35（19.4%）	40（22.2%）	16（8.9%）
Placebo (N=175)	27（15.4%）	46（26.3%）	51（29.1%）	31（17.7%）

Confirmed risk reduction for each neurological symptom

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P value by Fisher's exact test *<0.05

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Here are four neurological symptoms. These situations also confirm a downward trend. When it came to insomnia, 31 people had complaints of insomnia on placebo, and we were able to confirm a statistically significant reduction in risk in the form of a reduction to 16 people by injection of ensitrelvir.

Summary of Results

- **Phase 3 part of Phase 2/3 trial was conducted in patients with mild/moderate COVID-19**
  - ✓ Approximately 90% of patients were vaccinated against SARS-CoV-2 and infected with Omicron
  - ✓ With or without high-risk factors
- **Early improvement of COVID-19 symptoms by administration of ensitrelvir**
- **Confirmed potent antiviral activity**
  - ✓ Significantly reduced time to infectious virus negativity compared to placebo
  - ✓ Nearly all patients (96%) had negative viral titers on Day 4 (after 3 doses) compared to placebo
- **Reduction of the risk of Long COVID manifestation**
  - ✓ Significantly reduced risk of Long COVID manifestation in severely symptomatic patients versus placebo
    - 45% reduction in the proportion of patients with long-lasting any of the 14 symptoms characteristic of COVID-19
    - 33% reduction in the proportion of patients presenting with the four most commonly reported post-acute neurological symptoms
- **No safety concerns were identified; ensitrelvir was well tolerated**

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Note) The figures in red are newly announced results

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Let me summarize. We were able to test the study in a manner that reflects actual clinical practice, with or without vaccination, and with or without risk factors in patients with mild disease, moderate disease, and those who did not require inpatient care.

In this context, in terms of how antiviral agents can be utilized, the first is to improve symptoms at an early stage. It then shows an antiviral effect, stopping the body from expelling the live virus as quickly as possible. Furthermore, the results suggest that the risk of developing Long COVID is also reduced.

Since this is an exploratory evaluation, we would like to disclose the data in a timely manner, taking into account the one-year follow-up data and other comprehensive data.

The SCORPIO-HR study of active study, being conducted globally, will also evaluate Long COVID, and we hope to gradually accumulate data on the presence or absence of Long COVID in placebo subjects in a prospective manner.

By the way, some of you may be aware, this examination does key break. The keys are only disclosed internally. Therefore, the key is not shared with the doctors at the facilities or patients. The evaluation of Long COVID is under so-called “blind” conditions.

The following appendix summarizes the English version of the CROI slides.

That’s all from me.

Question & Answer

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

The first question comes from Mr. Ueda, Goldman Sachs Securities.

Ueda : I'm Ueda from Goldman Sachs Japan.

First, I would like to ask about the after-effect. I assume that the data in this study was analyzed within 120 hours of administration. For example, can you tell us if there is any benefit to administering the drug earlier in the post-analysis period, such as within 72 hours or within 72 hours to 120 hours?

Uehara : Thank you for your question. We collect data from voluntarily submitted reports on Long COVID symptoms, but we have not been able to collect data from all patients.

Roughly 50% or 60% of the patients responded. Therefore, we have disclosed the overall data because the sample size would be very small if we break it down further.

As for the overall trend, there is no significant difference as far as we can easily ascertain. I also had a hypothesis that it might be more effective within 72 hours.

However, there is not much difference in the trend, and the data may suggest that patients who came to the hospital for medication can reduce the risk of remaining symptoms by taking the medication, even if the overall population has passed the 72-hour period. I interpret the data as suggesting that the risk of such symptoms persisting can be reduced by still taking the medication, even if the 72-hour period has passed.

Ueda : Thank you very much. The second question is about the viral titer data. I would like to know if there is any research you have done on relapse or high risk of re-infection.

Uehara : Thank you. As you can see, at the time of Day Nine, the titer has already gone negative at Day Nine, but basically, there are no patients whose viral titer has rebound after this point.

We plan to disclose detailed data on relapse at the European Conference on Communicable Diseases, or ECCMID, which will be held in April. The doctors and researchers in CROI conference hall were very interested in the relapse and asked many questions about it. There are of course some accidental noises in the overalls. However, I have a feeling that there may not be a significant rebound risk with the overalls, nor a risk of symptom flare-ups, as I answered during the Q&A session on the floor.

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

Kyokawa : Thank you. The next question comes from Mr. Kohtani with Nomura Securities, please begin.

Kohtani : I'm Kohtani from Nomura Securities.

Thank you for showing us the wonderful data. I am just a little concerned about this, but this is the content of an exploratory study, so as you said, it is not intended to be statistically significant. It is indeed great data, but it is probably difficult to say whether this can be put on the label.

What I am concerned about is that this study might end up as a mere reference. You mentioned that only about 50% of the patients submitted the survey. If that is the case, would that lead to a sampling bias? Are you selectively reporting only those with multiple symptoms? I'm getting a little concerned about these. How will this data be handled?

I would also like to confirm that when you look at Long COVID in the SCORPIO-HR study, do you intend to use it for a pre-specified endpoint? That is my first question.

Uehara : Thank you very much. As you indicated, this is an exploratory analysis. In terms of whether or not this result will be included in the leveling, I do not think it will be applicable to a compound that lowers Long COVID risk as an application. In order to obtain such a leveling application, it is customary to implement the perspective for that purpose on a large scale. Our current plan is to accumulate a variety of evidence from a scientific perspective and disclose through publicity.

In terms of sample size, the concerns you mentioned cannot, of course, be completely eliminated. Although we do not see any particular bias in the overall background of the patients we have collected this time, we have not been able to collect data on all patients. There is a possibility that only those who have symptoms are responding.

Even if so, the fact that there is a trend that shows a difference between the two is a promising result.

The same is basically true for the global SCORPIO-HR exam. The main objective of the global study is to verify the improvement of symptoms in the global study, so Long COVID is being evaluated only as a secondary endpoint.

Kohtani : I have a second question. I would like to ask how the doctors who participated in the CROI reacted to this data, just as much as you know now. I think it is said that symptom improvement, even in the case of Tamiflu or Xofluza as an example, only reduces the duration of symptoms by 24 hours at most.

With the data that shows a reduction in dreadful after-effects, I am thinking that perhaps in Japan, such data alone would make it considerably easier to proceed with prescribing. Please let me confirm the impact of this data, in terms of CROI and whether Japanese doctors are moving in the right direction.

Uehara : As you can imagine, regarding the survey data, we didn't conduct hearing sessions with all doctors and the professors who were present at the conference. That said, we had discussions based on the data with NIAID professors, including Mr. Anthony Fauci, researchers, and other professors who are conducting HR trials globally.

As you just mentioned, they are strongly aware that there are many people who have these symptoms even if they are not at standard risk, and they hope that they are able to show the significance of using these drugs. The feedback we have received from them is that they are expecting the drug to have a positive effect.

Kohtani : I'm sorry. Lastly, just to confirm, have you seen this kind of data, or similar data, with molnupiravir and Paxlovid?

Uehara : With regard to Paxlovid, we compiled data from health insurance claims, and based on the medical database, we found that patients who took Paxlovid came to the hospital with some symptoms and that there was a possibility of reducing the risk of such patients by 20% to 30%.

However, the difference with our trial is that I don't think there is any published data obtained from any drug that I am aware of that directly compares data like this in a placebo-subject trial where the patient was treated.

Kohtani : It's clear. Thank you for the great data. That's all from me.

Kyokawa : Thank you very much. The next question comes from Mr. Yamaguchi of Citigroup Securities.

Yamaguchi : Good morning. This is Yamaguchi from Citigroup. Thank you.

I don't know the details of the study so this may be already covered in the presentation but let me ask this. First, when trial the patients with Long COVID symptoms, as they cope with various symptoms, did you track, including these placebo patients, any remedies specific to the symptoms?

For example, when someone has a sore throat, they may take sore throat medicine, or for insomnia, they may treat themselves with a sleeping aid. Were those treatments covered in the trial?

Uehara : We're talking about people who have completed the clinical trial. In other words, we didn't control what they may select to treat their symptoms on their own. So, some of the patients may use some form of medication, while some may just cope with mild sluggishness.

Yamaguchi : So you are saying you are not tracking those.

Uehara : Yes, that is correct.

Yamaguchi : I understand.

One more thing. I was also slightly confused for a moment in the earlier discussion, regarding the bias. If indeed there is any sort of bias, you mentioned that more people with multiple symptoms are potentially included in the report compared to people with fewer symptoms. This means people with no symptoms are not included in the study.

Does this make the data look better or worse than it actually is? Could you talk about the potential bias?

Uehara : I want to say that we do not have any data to dismiss the concern that people without symptoms may not be included in the study. In such a situation, if people who do not have symptoms are not included, the overall percentage will be smaller, but the difference will not disappear.

Yamaguchi : I see, thank you.

Finally, you introduced some of the discussions you had with doctors at the conference, including a question concerning relapse. Were there any other topics that were discussed during the Q&A session at the conference?

Uehara : We talked about the rebound of the antiviral effect. Furthermore, the doctors knew from the data that when the tapering period is long rebound does not occur. I commented after the presentation that the blood concentration can be maintained above the EC90 value with the prolonged tapering period for more than 10 days.

Regarding the primary endpoint, we only looked at 5 symptoms. I explained that I have noted a similar trend of shortening in both 12 symptoms and 14 symptoms, and that with 14 symptoms it shortened by two days with statistically significant differences. Some doctors nodded their heads in agreement.

I also received a question as to how we evaluate the disappearance of symptoms. I answered by describing that we let the patients log their symptoms in the format of a diary, and we instruct them to write the diary twice a day so that we can analyze the time it takes for the symptoms to disappear.

The duration of symptom resolution, which is also related to relapse, is also a factor, but in this trial, if the symptoms have been gone for 24 hours, the symptoms are considered to be gone.

In the global market, there are a variety of ideas, such as 96 hours or 48 hours, so I commented that the trend is the same even if we perform posterior analysis on various endpoints from this perspective.

Yamaguchi : I understand. I learned a lot. Thank you. That's all from me.

Kyokawa : Thank you. The next question comes from Daiwa Securities, Mr. Hashiguchi, please go ahead.

Hashiguchi : This is Hashiguchi from Daiwa Securities. Thank you for having me.

In this analysis, the patients with relatively high symptom scores at the start of the study tended to show a greater difference than the overall subject group.

You mentioned earlier that this relatively high symptom score is above the median. How can the score appear in actual clinical practice? For example, what severity of fever or cough are we talking about? Can you share some background on the patient who showed a stronger tendency this time?

Uehara : Thank you very much.

First, this symptom score is based on a scaling of 14 symptoms -- 0, 1, 2, and 3 -- where 1 is mild, 2 is moderate, and 3 is severe. We have taken 14 symptoms, which is more than nine, so even if there are nine mild symptoms, the median value will still be above the median, but that is rare.

In fact, many patients have some moderate or severe symptoms.

The message from this analysis of the data is this: if you are not experiencing any symptoms, nothing particular will happen to you after you are fully recovered. A lot of research on Long COVID has started. Initially, it was said that it is just a neurological symptom or just in the imagination, or something psychological.

One theory is that the virus is doing something in a specific domain of the human body. Various papers now discuss that macrophages and other viruses proliferate locally and that nerve cells are slightly damaged at

these localities. The virus increases in the respiratory epithelium of the upper respiratory tract, and that is the primary behavior of the virus before it gradually and progressively spreads to various parts of the body.

Consequently, I think, much like the case of taste and smell disorder, the virus can produce various symptoms where it increases and spreads in the body. This can be a risk to the human body.

Conversely, both the symptom and the spread of the virus can be stopped by taking medicine as soon as possible. I think that is what the results of the trial suggest.

Hashiguchi : Thank you. In that sense, was there a tendency to see differences in efficacy depending on the amount of baseline viral RNA?

Uehara : I would like to look at some data from that perspective, as you indicated. Incidentally, these results came out in early February, so we have not yet caught up on all the analysis and various angles.

The baseline virus that we are evaluating with the swab is only from the nose. So, it is not always possible to read from a nose swab how far the disease has spread. We would like to analyze it again and use it again for presentations, at some other occasion.

Hashiguchi : Finally, you mentioned earlier that the research was conducted as a part of an exploratory analysis, but what are your thoughts on conducting a verification trial? I imagine that you will have to consider the need for this data in the future as you see how it is received.

Uehara : You are right. If we can confirm these trends, we will need to conduct a separate trial if we want to verify them.

There is also the concept of company-initiated clinical trials, such as the one we are conducting. Or investigator-initiated clinical trial.

I think we can work on this from a variety of perspectives. We are now beginning discussions within our company on how to proceed in the future, based on the results of this study.

Hashiguchi : Thank you. That's all from me.

Kyokawa : Thank you very much. The next question comes from Mr. Sakai with Credit Suisse Securities.

Sakai : I am Sakai from Credit Suisse Securities in Japan. Thank you for taking my questions.

You mentioned labels earlier and now you are talking about the verification trial. What is your plan to make the most use of this data? Especially in Japan, at this stage, it is a little difficult to do something about it from a promotional point of view. I would like to ask you about the handling of this data on a premise that the ban on general prescriptions for Xocova is going to be lifted in the Japanese market.

Uehara : Thank you very much. First, regarding the treatment, the data here is an intermediate analysis. However, we would like to submit our data to some scientific journals. So, I am sure that through such papers, doctors will have the opportunity to be exposed to the data.

Sakai : I understand. As for the timing for publishing the paper, would that be based on future discussions within the Company?

Uehara : Yes. We can't just say, "oh, it should be available a year from now." Since this is an interim report, I think there is a chance that it could be issued quickly in the form of a short report with a concise flow. We are in the process of swiftly preparing the academic thesis.

Sakai : I understand. One more thing, regarding this data. The score in the taste and smell disorders. As you mentioned, the virus probably stays in this area, the respiratory system, and by excluding it, this 100% figure in relative risk for smell and taste disorders is obtained. I am sorry, this is an extremely short-sighted question, but is that correct?

The reason I ask is that many people who were infected with the virus think that the symptoms that affect taste and smell are the most annoying, or distressing, among all Long COVID symptoms.

What are your assessments?

Uehara : I have the same feeling. Before Omicron epidemic spread, taste and smell disorders were very much in the news, and I think many people are now aware that taste and smell abnormalities do not occur. But that perception may not be correct.

In fact, even during the 21 days of follow-up of the clinical trial, some patients showed taste and smell disorders, while others did not. Some had baseline taste and olfactory abnormalities. It has been consistently confirmed in both Phase 2 and 3 that the risk of showing abnormalities in taste and smell is clearly lower if the medication is taken for 21 days.

Even with medication, it is obviously difficult to immediately cure a disease that has already occurred. Because it is a sensory organ. I think that the virus has reached the cells of the sense of taste and smell before it occurs, which is probably a hypothesis.

It is possible that such inflammation spills over and weakens the cells of the sensory organs of taste and smell, perhaps even weakening their function slightly. We interpret the results as stopping the growth of the virus in its early stage with drugs may reduce the risk of these taste and smell sensations, and also reduce the risk of these sensations continuing to occur later in life.

Sakai : I understand. Thank you.

One last thing, aside from the result of the research, regarding STRIVE. Since you are talking about targeting hospitalized patients, considering the current infection situation, how much patient enrollment will progress? I think you use 350 milligram doses and 125 milligram doses, and I'm curious to learn about a particular reason for using 350 milligram doses. That's all from me.

Uehara : Thank you very much. As for STRIVE, there are contraindications to enrolling in terms of taking various medications together, so there are certain people who may not be able to participate in this trial. It has just started, and we are still waiting to see how quickly patients will be registered.

In fact, this all depends on the epidemic trend. There seems to be no doubt that the risk of serious illness is decreasing. However, the number of people dying from COVID-19 is by no means decreasing drastically because the number of contracted people in the population is increasing.

In this situation, considering that some neutralizing antibody drugs are no longer useful, doctors are very hopeful that these new drugs marketed for their anti-viral effects can help patients, more than what the current standard of care procedures can achieve. NIH doctors are very excited about the possibility of starting this project.

Therefore, we would like to accumulate data as soon as possible and have its effectiveness evaluated.

As for the dosage, you mentioned 350 milligrams, but actually it is 375 milligrams. Specifically, we administer three doses of one unit over 125 milligrams. This is Day One. Between Day Two and Day Five, we administer 125 milligrams, which is one tablet.

As to how we determine the dosage, again, this is true for 2a, 2b, 3, and all the trials, but the antiviral effect does not change at all at the low or high dosage.

In fact, this low dose has already demonstrated sufficient antiviral efficacy, so the global doctors felt that there was no need to go to the trouble of doubling the dosage to 750 milligrams.

Therefore, in the SCORPIO-HR study and the STRIVE study shown on this slide, all of these global studies were evaluated with a single dose of 375/125 milligrams, which is the approved dose in Japan.

Sakai : I understand. Thank you very much.

Kyokawa : Thank you very much. The next question comes from Mr. Wakao with JP Morgan Securities.

Wakao: This is Wakao from JP Morgan. Thank you for this opportunity.

First, please let me know if the results of this study have revealed anything like the characteristics of patients who are more likely to develop Long COVID and those who are better responders.

I somehow understood from this presentation that people who are more likely to develop the disease are those with higher symptom scores. Also, in terms of good response, I think you mentioned that the onset time is not relevant, like within 72 hours. Could you please sort out this area?

Uehara : This is exactly what we have shown you this time, and the most distinctive feature is this symptom score. We have shown that people with severe symptom scores are more likely to be at Long COVID risk.

As is generally the case, women tend to have more severe symptoms than men, as seen in the duration of the disease, and I have a feeling that there may be a tendency to do so in the Long COVID area.

We will do additional analysis on the various data and disclose them in a timely manner, but the one that shows the most difference is the baseline symptom score here.

Wakao : What are some of the characteristics of a person who is responsive? For example, what else can you say about that part?

Uehara : It is difficult to say whether those who respond well are those whose symptoms are cured immediately and who do not have Long COVID, or whether those whose symptoms are cured immediately and not just Long COVID are those whose symptoms are cured immediately and why. We do not have any data to answer this question clearly at this point.

Wakao : Thank you very much. Looking at the 250 milligrams data you attached to the Appendix, I wonder if the data is better for the 125 milligrams. Why is the data here not so good for 250 milligrams and better for 125 milligrams? I think 250 milligrams was faster, as far as the speed of [Inaudible] to the virus. How should this be interpreted here?

Uehara : I received the same question at CROI. My immediate answer was that I don't know. Basically, and I repeat this, I have read that the antiviral effect is the same at both low and high doses. You may have seen the red and blue graphs that often overlap as data.

As for the effect of antiviral drugs, it does not matter either way. Therefore, it would be better to look at the data as if the two were added and divided by two, and read it as if the sample size had increased by that amount.

We also had discussions internally. In fact, depending on the endpoint, the higher dose may be better, and for the time for the symptom resolution in the Phase 3 trial, the higher dose may have been more effective. We are doing two different doses, so there are a variety of results.

My interpretation is that there is no need to view this as a major difference.

Wakao : Thank you very much. Finally, pages 16 and 17 of the slides discuss why it tends to work well for taste and smell disorders, which were well discussed in earlier questions.

Considering the mechanism of this drug, it works well for taste and smell, but for neurological symptoms, for example, I think we still don't know the mechanism by which these neurological symptoms develop in the first place, but should we take it as relatively ineffective for these neurological symptoms?

Uehara : Taste and smell disorders are characteristic symptoms that you don’t experience often unless you have COVID-19. Therefore, it can be considered as data of low noise.

In contrast, the neurological symptoms I mentioned earlier, such as poor concentration and memory loss are also included in the voluntary questionnaire, but I think there is probably a lot of noise. There are probably some people who think that since they infected COVID-19, they have become forgetful about such things, so please understand that this evaluation takes such noise into account.

Wakao : It’s clear. Thank you. That's all from me.

Kyokawa : The next question is from Mr. Tsuzuki of Mizuho Securities, please.

Tsuzuki : My name is Tsuzuki of Mizuho Securities. Thank you.

First, congratulations on the viral titer results. This means that the risk of secondary infection can be suppressed to a great extent, so I’m sure that the drug is quite useful even when it is Class Five. Thank you.

One point is regarding the Paxlovid comparison. When Paxlovid was done in the US, based on data from about 60,000 people, it showed about a 26% reduction in Long COVID, and as for your company, it was a 25% reduction, and for those with higher symptom scores, it was a 45% reduction, so I would say it is comparable, or rather higher, because there is a placebo comparison.

But on the other hand, I think the small number of people is a concern. In order to raise the number of patients, I would like to know when the Long COVID symptom data for patients in Japan will be available.

Uehara : Thank you very much. As you are already aware, our company is also planning to conduct a database study to see how we can aggregate data from the people who are currently taking Xocova and will continue to show the risk of Long COVID.

However, since this is a Long COVID, it will take three months or six months, so please be aware that the results will not magically appear tomorrow.

Tsuzuki : I see. More data would be appreciated, as I believe that Japanese doctors are quite demanding.

Also, one more point. Molnupiravir, for example. The emergence of resistant strains has been talked about quite a lot in the pre-peer review papers, but what is the current status of this Xocova, if anything?

That is all from me.

Uehara : Thank you very much. As you are already aware, the drug is effective against the strains that are currently prevalent, so there are no resistant strains prevalent.

Regarding the risk of isolating resistant viruses by performing post-drug sequencing, we are in the process of sequencing now. We will analyze the clinical trial data very carefully and will disclose such data as soon as the results are available.

Tsuzuki : Okay. Thank you very much.

Kyokawa : Since that seems to be all the questions we have, I would like to wrap up this meeting.

Thank you for joining the SHIONOGI CROI 2023 Follow-up Meeting. We appreciate your time.

[END]