SHIONOGI & CO., LTD.

ESWI 2023 Follow-up Meeting

September 19, 2023

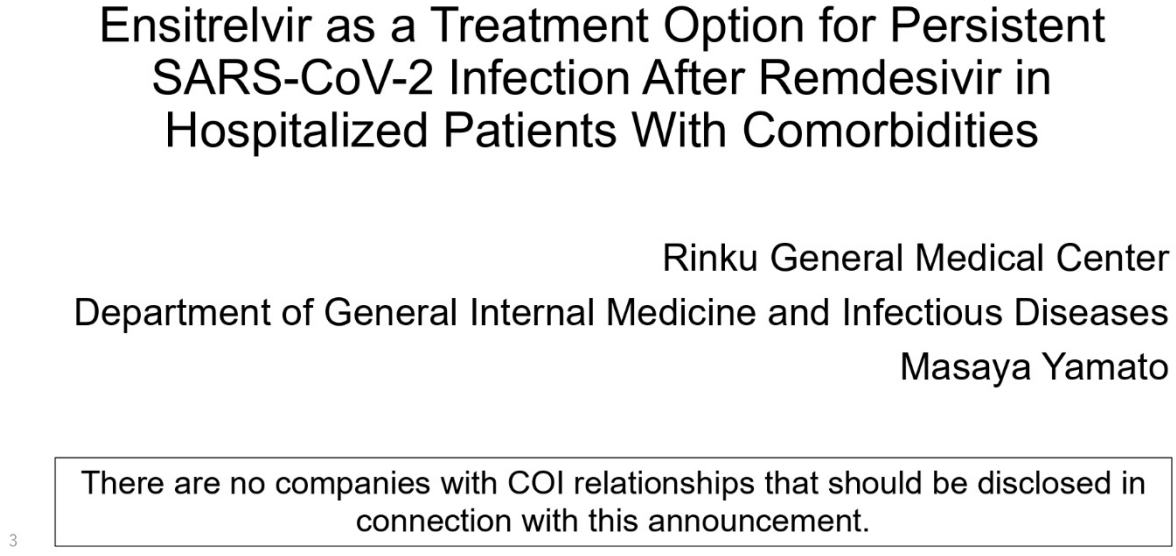
Presentation

Kyokawa: My name is Kyokawa, Vice President of Corporate Communications Department of SHIONOGI & CO., LTD. Thank you very much for joining us today despite your busy schedule. We now begin the ESWI 2023 Follow-up Meeting. Today we would like to present new data on ensitrelvir presented at ESWI, currently taking place in Valencia, Spain.

First, let me introduce today's speakers. This is Dr. Masaya Yamato, MD, Infectious Diseases Center Director at Rinku General Medical Center. This is John Keller, Senior Executive Officer, Vice President of the R&D Supervisory Unit and Investment Strategy Department. This is Takeki Uehara, Senior Vice President of the Drug Development and Regulatory Science Division.

Kyokawa: Dr. Yamato and our company, Uehara, are participating from Valencia. As for today's schedule, Dr. Yamato will first present the results of treatment of hospitalized patients with risk factors for severe disease by switching from remdesivir to ensitrelvir. After that, Mr. Uehara will explain the results of the exploratory evaluation of the Phase II/III clinical trial in Japan on the effect of ensitrelvir on Long COVID at one year post-hoc analysis. A question & answer session will follow. The event is scheduled to end at 9:00 AM.

Let us begin immediately. Thank you very much, Dr. Yamato.



Yamato: Hello everyone.

My name is Yamato, and I am the director of the Infectious Disease Center at Rinku General Medical Center in Osaka. There are no companies with COI as stated there.

Background and Purpose

Ensitrelvir

- Ensitrelvir is an oral inhibitor of 3 CL protease of SARS-CoV-2 approved under the emergency regulatory approval system in Japan
  - Ensitrelvir has shown early alleviation of symptom and cessation of viral shedding in patients with mild-to-moderate COVID-19

Current status of ensitrelvir

There is insufficient evidence regarding the efficacy and safety of ensitrelvir in patients suffering from persistent COVID-19, those with comorbidities, and hospitalized patients.

Purpose of trial

To assess the clinical outcomes, including background and treatment outcomes, of hospitalized patients with risk factors for severe disease who were treated with ensitrelvir in Japan

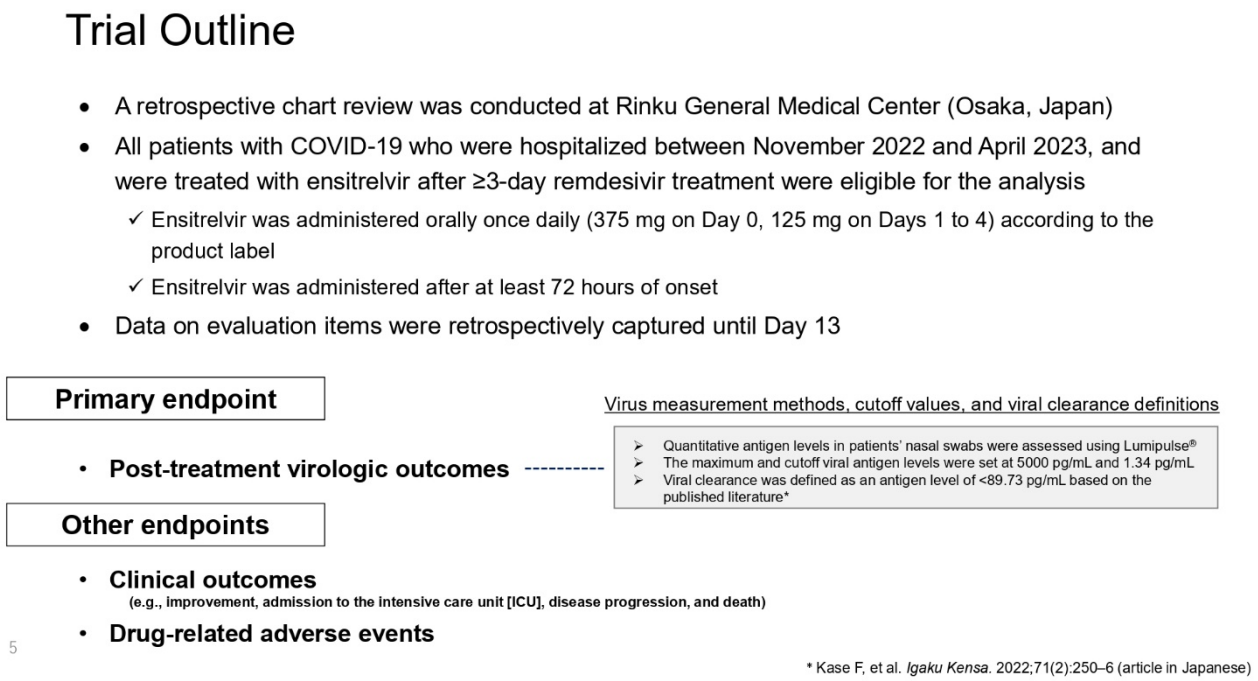
(UMIN Clinical Trials identifier: UMIN000051300)

Background and purpose.

Ensitrelvir is 3CL protease inhibitor that was approved under the emergency regulatory approval system in Japan to treat COVID-19. Ensitrelvir has shown early alleviation of symptom and cessation of viral shedding in patients with mild-to-moderate COVID-19ding.

Currently, there is insufficient evidence regarding the efficacy and safety of ensitrelvir in patients suffering from persistent COVID-19 symptoms, those with comorbidities, and hospitalized patients.

The purpose of this study was to assess the clinical outcomes, including background and treatment outcomes, of hospitalized patients with risk factors for severe disease who were treated with ensitrelvir in Japan.



This is a summary of the trial.

We have conducted a retrospective chart review at Rinku General Medical Center in Osaka, Japan. All patients with COVID-19 who were hospitalized between November 2022 and April 2023, and were treated with ensitrelvir after ≥3-day remdesivir treatment were eligible for the analysis.

Ensitrelvir was administered orally for five days once daily, three pills of 375 mg on Day 0, one pills of 125 mg on Day 1 to Day 4 according to the product label. Ensitrelvir was administered after at least 72 hours of onset. Data on evaluation items were retrospectively captured until Day 13.

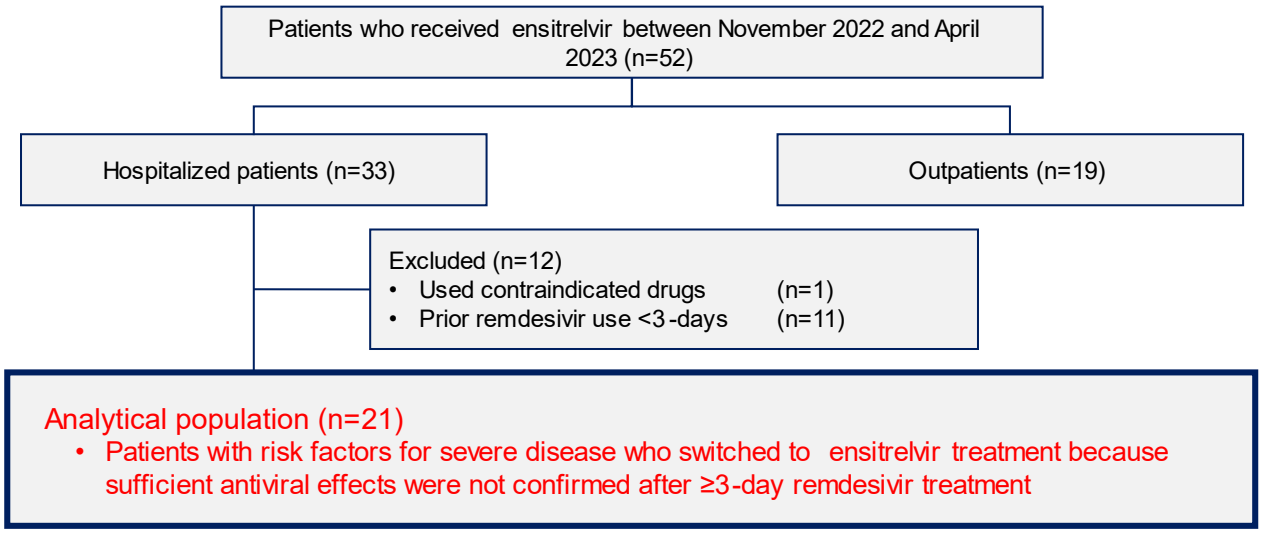
First, the primary endpoint. We are looking at post-treatment virologic outcomes. The virus is evaluated by quantitative antigen level in this study. Here it describes the virus measurement method, cutoff values, and viral clearance of the quantitative antigen.

Quantitative antigen levels in patients' nasal swabs were assessed using Lum pulse. The maximum and cutoff levels of viral antigens are respectively 5,000 over-range with a cutoff of 1.34 pg/mL, which is in accordance with the manufacturer's accompanying documentation.

However, as for viral clearance, it is often said that one of the guidelines to determine whether or not an infectious virus is isolated is PCR CT value of 35. The equivalent level of an antigen level to it is less than 89.73 pg/mL. We have adopted the report from Japan in our research as shown on the lower right corner.

In addition to these virologic outcomes, we also check for clinical outcomes, improvement, ICU admission, disease progression, death, and other more serious progression. We have also checked the occurrence of adverse events due to the administration of ensitrelvir.

Patient disposition



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This is patient disposition.

There was a total of 52 patients treated with ensitrelvir from November 2022 to April 2023, in our clinic. Among them, 33 were inpatients, excluding 19 outpatient cases. 12 patients were further excluded as shown below: One patient used contraindicated drugs, and 11 patients used remdesivir for less than three days. The analytical population for this presentation thus includes 21 patients, including 12 cases of those were on ensitrelvir from the beginning.

Adequate antiviral efficacy has not been confirmed after remdesivir treatment for more than three days. In that sense, switching to ensitrelvir is the use in this study. So I would like to show on the following slides what the outcomes are and what the viral trends are in patients with risk factors for severe disease who have been switched to ensitrelvir treatment.

Patient Demographics and Clinical Characteristics on Day 0

	Overall (n=21)	Mild (n=17)	Moderate I (n=2)	Moderate II (n=2)
Male sex, n (%)	10 (47.6)	6 (35.3)	2 (100.0)	2 (100.0)
Age (years), mean ± SD	78.0±8.9	77.4±8.4	73.5±12.0	87.5±9.2
Prior treatment for SARS-CoV-2 infection, n (%)				
Remdesivir	20 (95.2)	16 (94.1)	2 (100.0)	2 (100.0)
Remdesivir + casirivimab/imdevimab	1 (4.8)	1 (5.9)	0 (0.0)	0 (0.0)
Duration of remdesivir treatment (days), mean ± SD	6.6±3.9	6.5±4.2	7.5±3.5	6.0±2.8
No SARS-CoV-2 vaccination, n (%)	5 (23.8)	4 (23.5)	0 (0.0)	1 (50.0)
Concomitant use of systemic corticosteroids, n (%)	5 (23.8)	5 (29.4)	0 (0.0)	0 (0.0)
Comorbidity, n (%)				
Malignant tumors	7 (33.3)	6 (35.3)	0 (0.0)	1 (50.0)
Diabetes mellitus	6 (28.6)	2 (11.8)	2 (100.0)	2 (100.0)
Renal failure	4 (19.0)	3 (17.6)	0 (0.0)	1 (50.0)

COVID-19 disease severity criteria (according to Japanese guideline)

Severity	SpO_2	Clinical condition
Mild	$SpO_2 \geq 96\%$	No respiratory symptoms or cough only (no dyspnea, no evidence of pneumonia)
Moderate I	$93\% < SpO_2 > 96\%$	Dyspnea, pneumonia
Moderate II	$SpO_2 \leq 93\%$	Requires oxygen
Severe		ICU admission or requires mechanical ventilator

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First, let me explain the main patient backgrounds of the enrolled cases.

In Japan, as you may be aware, the severity of COVID-19 is defined by the treatment guidelines issued by the Japanese Ministry of Health, Labour and Welfare. As it is shown in the lower right corner, SpO_2, or degree of oxygen saturation, 96% and above without pneumonia is considered mild case. Severe is defined as ICU admission or requires mechanical ventilator. Moderate is defined in between mild and severe .

But when there is pneumonia, those who need oxygen, or have respiratory failure and SpO_2 93 and under is considered moderate II. Moderate I is SpO2 level from 93% to 96%, with no respiratory failure even if there is pneumonia.

Be in mind on this clinical characteristics, let's look the following figures show the gender and percentage of patients. 17 patients out of 21 patients are in mild category, then moderate I and moderate II, respectively shown in the table.

The average age of the patients was 78 years old. As for the treatment of COVID-19 prior to the administration of ensitrelvir, all 21 patients were treated with remdesivir, of which one patient received the neutralizing antibody drug casirivimab and imdevimab.

The duration of treatment with remdesivir is generally three days for mild cases and five days for moderate cases. In this case, the overall duration was 6.6 days ± 3.9 days, which is 6.5 days for mild cases, 7.5 days for moderate I cases, and six days for moderate II cases, and the dosage was in accordance with the guideline.

For those who have not been vaccinated against COVID-19 were 5 out of 21 cases, or 23.8% of the total. Therefore three-fourths have been vaccinated.

There are various factors that can be used as indicators of immunosuppression, including the use of systemic corticosteroids in five cases due to the underlying disease. In addition, the evaluation of the linkage factors of patients at high risk of severity of illness is included in the table, but there are seven patients with malignant tumors, six with diabetes, and four with renal failure. I think it would be safe to understand that this is transition from remdesivir who have severity of illness.

Antiviral Effect of Ensitrelvir

Confirmed strong antiviral effect in patients with risk factors for severe disease

patients	Last remdesivir dose	Remdesivir treatment period (days)	Individual patient characteristics and viral antigen levels (pg/mL)														
			Ensitrelvir administration period														
			Day-2,-1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13
1	Day 0	8	5000	5000		5000	5000	5000				1233	495		255	8.67	44.6
2	Day 0	4	5000	5000			87.07	25.39	8.5	6.81	7.94	94.59	0.14	2.29	0.05	1.73	0.57
3	Day -2	5	206	3430	235	10.35	1.06	0.95									
4	Day 0	10	5000	5000			538		84.4	7.89	43.06	3.56	2.08	0.01	0.06		
5	Day -1	5	5000	5000		571			21.75	18.67	9.43	2.81	0.06	4.79	0.01	0.1	
6	Day -1	5	255	5000			36.55		25.72	1.61	0.3	0.01					
7	Day -1	5	5000	5000		1394		39.12	43.49	46.3		28.65	0.83	0.89			
8	Day 0	4		5000		1676					27.73						
9	Day -1	8	5000	2729	3736	142		13.5	0.3								
10	Day 1	22	5000	5000		2588		4.77	1211		5000	5000	5000				
11	Day 0	8	5000	5000	5000		1087	4091			16.27	11.83	3.76	1.73	0.01		
12	Day -1	7	5000			1.04	0.11										
13	Day -1	6	5000	5000		53.22			2.1	0.62							
14	Day 0	5	4329	5000		5000			2468		5000		3637			114.93	12.95
15	Day 0	5	1728	2393		1354			2.51	1.61	1.05	2.59	1.03	0.01			
16	Day -6	5	5000		5000			7.42	8.09	1.97	4.39	0.71	2.78	0.67	1.72	0.08	0.24
17	Day 0	3	5000	5000			224		2.37	8.01	5.99	41.02		1.23	0.01		
18	Day -1	7	1305	5000			1021				19.95	1.89	0.57	0.24			
19	Day -1	6	5000			1767	275	246	148	111			3.44	6.81	1.92	1.15	0.56
20	Day -2	5	5000	5000		5000		1330									
21	Day -1	5	5000	5000		1292			63.29		9.86	11.31	1.56	0.01			

Red : Areas where virus clearance has not been achieved （ > 89.73pg/ml）
: Period the patient has been in the hospital
: The day when viral clearance was achieved by the next day of ensitrevir treatment

Viral clearance was achieved in 66.7% (14/21 patients) of patients by the next day after ensitrelvir treatment

Now I would like to present the antiviral effect of ensitrelvir and the actual Lumipulse values for all cases.

the patient number of 1 to 21, the leftmost columns show the date of the last remdesivirdose and day of its administration. Even if you use it for 22 days, even if you use it for that long, it doesn't go down enough to rise to the upper range. Or we use ensitrelvir for the case that has rebounded to that point. The dosing period of ensitrelvir is five days in all cases as per the package insert.

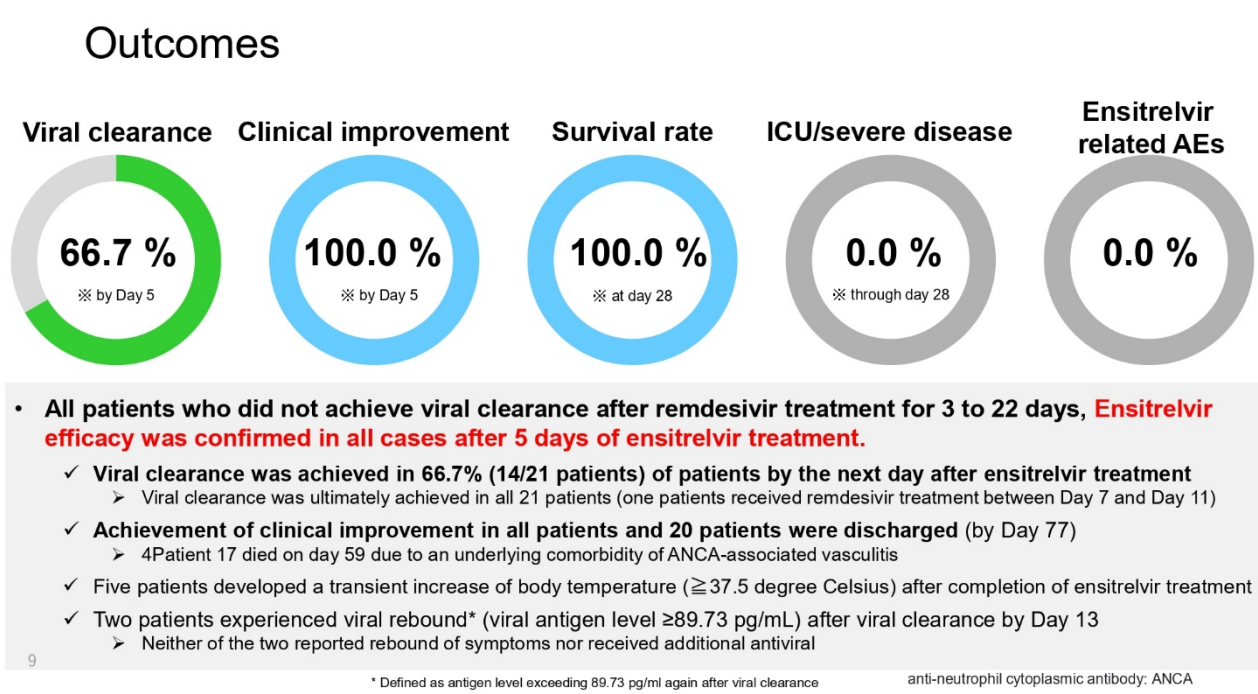
The green circled figures explained on the lower left are those who achieved viral clearance by the day after the ensitrelvir treatment. Although we have set a rather strict figure, there were 14 cases out of 21 that were circled in green by the next day of the five-day period. This means that two thirds of the patients have achieved viral clearance, which means that the infectious virus is presumed to have disappeared from the body.

However, in other cases as well, for example, in the case of patient number one, even after administering ensitrelvir, the virus did not drop from the level of more than 5,000. When we carefully observed the clinical symptoms of the patient, the symptoms were improving, and even in this case, the virus titer was estimated to be negative on Day12.

Then there is patient number eight, which was not achieved in the five days, meaning by next day after the ensitrelvir treatment, but on the seventh day, viral antigen levels was 27pg/mL, which is less than 89pg/mL.

In patient number 11, the green circle number indicates that the titer had not reached viral clearance by Day5, but on Day7 it was 16.27pg/mL, which means that the patient was confirmed to be negative at the end of the study. This case was confirmed to be negative at the end, but from the point of view of viral titer, viral clearance was achieved on Day7.

So, there are no cases of worsening of overall clinical symptoms, and I think we can show that even if viral clearance is not achieved by Day5, it is achieved by the second week in almost all cases.



This is a summary of the results of this study.

In terms of viral clearance, the number of viruses that are expected to enter human infectious virus isolation culture, in another words, those that have achieved an antigen quantitative value of 89, is 66.7%, or two-thirds of the total. It was achieved by next day after five days of treatment.

As for clinical improvement, it is 100% clinically improved. This was accomplished by next day after the five-days treatment.

The survival rate is 100% because of clinical improvement, of course, and all patients were alive at Day 28 after the start of treatment.

And, of course, there were no ICU admissions, no serious illnesses, and no specific adverse events attributed to ensitrelvir.

To reconfirm, let me explain the details of the results of patients who did not achieve viral clearance after 3 to 22 days of treatment with remdesivir, the efficacy of the treatment was confirmed in all of those cases after five days of treatment with ensitrelvir.

By the day after five days treatment with ensitrelvir, 66.7% of patients had achieved viral clearance. We have confirmed that viral clearance was achieved in all 21 cases and in all patients in the end. All patients improved their clinical symptoms, and 20 were discharged from the hospital. There was a case that took up to 77 days, but the patient was hospitalized and discharged for the treatment of their original underlying disease.

However, there was one patient who died on day 59 due to underlying ANCA-associated vasculitis, although he had achieved viral clearance for COVID-19, had been confirmed negative twice, and was out of quarantine.

In five patients, there was a temporary increase in body temperature above 37.5 degrees Celsius after completion of ensitrelvir treatment. From a clinical point of view, the patients did not have any particular difficulty in breathing or general malaise.

Two patients experienced viral rebound by Day 14 of treatment, but no clinical rebound was observed, and no additional antivirals were needed.

Conclusion

- This trial was conducted in hospitalized patients who showed persistent SARS-CoV-2 infection after remdesivir and switched to ensitrelvir treatment
  - ✓ Hospitalized patients with comorbidities
- Ensitrelvir showed potent antiviral efficacy, and all patients improved clinically after ensitrelvir treatment.
- High efficacy confirmed for patients with risk factors for severe disease
  - ✓ No patients were admitted to the ICU due to severe disease through Day 28 period
  - ✓ Survival rate at day 28 is 100%
- Confirming the efficacy and safety of ensitrelvir even when treatment starts after 72 hours

These results indicate that ensitrelvir is a treatment option for patients with persistent SARS-CoV-2 infection and risk factors for severe disease

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This trial was conducted in patients who switched to ensitrelvir treatment after remdesivir treatment. Target patients were hospitalized and have comorbidities.

Ensitrelvir has a potent antiviral effect, and all patients show clinical improvement at the end of ensitrelvir treatment.

In addition, high efficacy has been confirmed for patients with risk factors for severe disease. Throughout the 28 days, no patient was admitted to the ICU due to severe disease. Survival rate at Day 28 was 100%.

It is significant that we were able to confirm the efficacy and safety of ensitrelvir treatment even in patients who started treatment with remdesivir with negative viral titers or viral rebound, or in patients whose symptoms did not improve, or in another words, whose treatment was started more than 72 hours after the onset of symptoms.

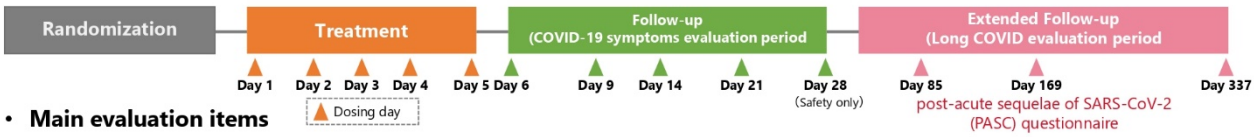
The final conclusion is that these results suggest that ensitrelvir can be a treatment option for COVID-19 patients with risk factors for severe disease.

That is all. Thank you very much for your attention.

Kyokawa: Thank you very much, Dr. Yamato. Next, Uehara will give a presentation. Please.

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



- **Main evaluation items**
  - Primary endpoint：Time to resolution[a] of five key Covid-19 symptoms
  - Key secondary endpoint：antiviral effect（viral RNA amount、virus titer)
  - Safety（Until the Day 28）
  - Exploratory endpoint: Presence of Long COVID symptoms evaluated by PASC questionnaire (27 symptoms)
    - Data up to Day 169 has already been reported at CROI 2023 in February 2023, and data up to Day 337 is the subject of this report

12 [a] Time to return to pre symptomatic state, defined as time to "recovery" in the trial protocol

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Uehara: Thank you very much. My name is Uehara.

As you are well aware, this is results of the Phase III part of Phase II/III, which was conducted mainly in Asia and Japan. In February of this year, 2023, we reported the results of the exploratory endpoint of Long COVID up to six months, specifically the results up to the two points in the exploratory phase, Day 85 and Day 169, shown in pink on the right side of this page, at the CROI meeting in the US.

The results of the Day 337 one-year follow-up evaluation has now been released at the ESWI conference, and we presented the results at conference.

Summary of 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 patients who completed the PASC questionnaire for at least one timepoint in the Intention-To-Treat (ITT*) population

	125 mg N = 341	Placebo N = 333
Male sex (%)	54.8%	58.3%
Age (years)	36.4	35.6
BMI (kg/m^2)	23.3	22.8
SARS-CoV-2 vaccination received	91.5%	92.8%
Total score of 14 symptoms[a] at baseline		
N	334	326
Median (range)	9.0 (1–30)	9.0 (2–28)

* 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)

[a] Stuffy or runny nose, sore throat, shortness of breath, cough, low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, nausea, vomiting, diarrhea, loss of smell, and loss of taste. Each symptom was self-assessed using a 4-point scale of 0 to 3 (3-point scale of 0 to 2 for loss of smell and loss of taste).
BMI, body mass index; range, minimum-maximum

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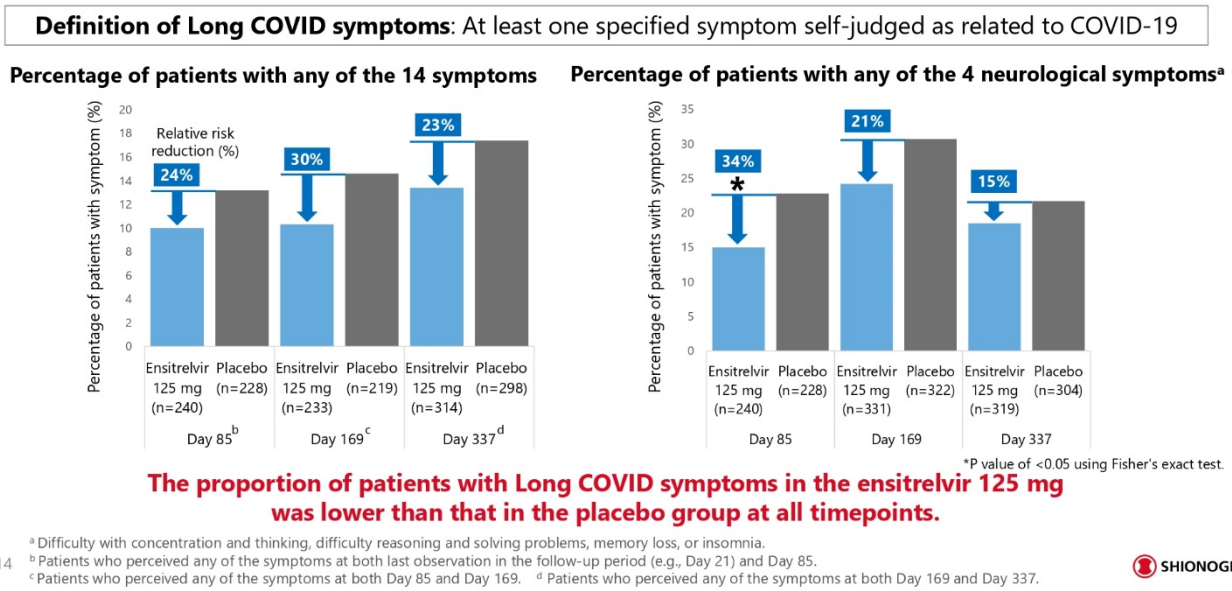
Here are the patients who responded and cooperated with the survey, especially regarding Long COVID for a total of one year.

Again, although this trial was conducted after key-breaking, the physicians at the facility and the patients themselves are not informed of whether or not they are on the actual drug. So, the survey related to Long COVID was conducted under blind conditions. We have received responses from more than 300 people in the past. As you can see, the average age is 36 years old, such a large number of people with no risk factors.

Therefore, the results were evaluated in a population that reflects actual clinical practice and almost all patients have received vaccine and are relatively young age.

Proportion of Patients with Long COVID Symptoms and Effect on Long COVID Symptoms



Here is the update data, from left to right: three months, six months, and Day 337 is one year.

Patients with at least 1 of the 14 COVID-19 acute symptoms are shown on the left side. On the right side, you can see the percentage of patients with neurological symptoms such as memory loss and poor concentration which are typical neurological symptoms.

As you can see, the percentage of patients with Long COVID who took ensitrelvir at three months, six months, and now the additional one-year time, becomes lower.

We adopted the Long COVID method of definition used in the CROI presentation at this year's conference. So, the method to collect survey was that we asked patients who had at least 1 of the 14 symptoms or 4 symptoms, to answer yes or no to the question of whether they thought they had a relationship with COVID-19. We are tabulating the results of the surveys, picking up answers that the patients said were relevant to COVID-19, but there are debates about how patients can make accurate evaluation after a year has passed.

In fact, if you look at the placebo group, there is a slight increase. Now the question is if the risk of Long COVID increases with the placebo arm over time? It is probably not. There are bunch of noises, but we have looked at it from various angles, and there seems to be no doubt that the risk is reduced by administering the actual drug. This time, we have additionally examined how we should evaluate it.

Proportion of patients who did not return to usual (pre-COVID) health

Patients who answered "No" to the question "Have you returned to your usual (pre-COVID) health?".

	125 mg N = 379	Placebo N = 362
Day 85	7.5% (18/240)	11.8% (27/228)
Day 165	7.6% (25/331)	10.2% (33/322)
Day 337	6.0% (19/319)	8.2% (25/304)

The proportion of patients not having returned to usual health in the ensitrelvir treatment group was lower than that in placebo group at all the timepoints.

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Another data we took in the survey was whether the patients had returned to pre-COVID health level. This was a yes or no question.

As you can see, compared to the placebo group, a lower percentage of those who took ensitrelvir at any point in time reported that they had not returned. In other words, the results are suggesting that patients quickly returned to the same health status as before getting COVID-19.

Revised definition of Long COVID

- Due to the following reasons, we have revised the definition to be more rigorous, considering that the previous definition may not be suitable for assessing long-term Long COVID over the period of a year.
  - Patients may not be able to accurately assess the relationship to COVID-19, especially at later time points (Day 337)
  - Some KOLs suggest that "patients who did not return to usual (pre-COVID) health" should be included in the definition

Before revision	After revision
Presence of at least one mild or more severe symptom, and has at least one symptom that self-judged as related to COVID-19	Presence of at least one mild or more severe symptom, not having returned to usual health

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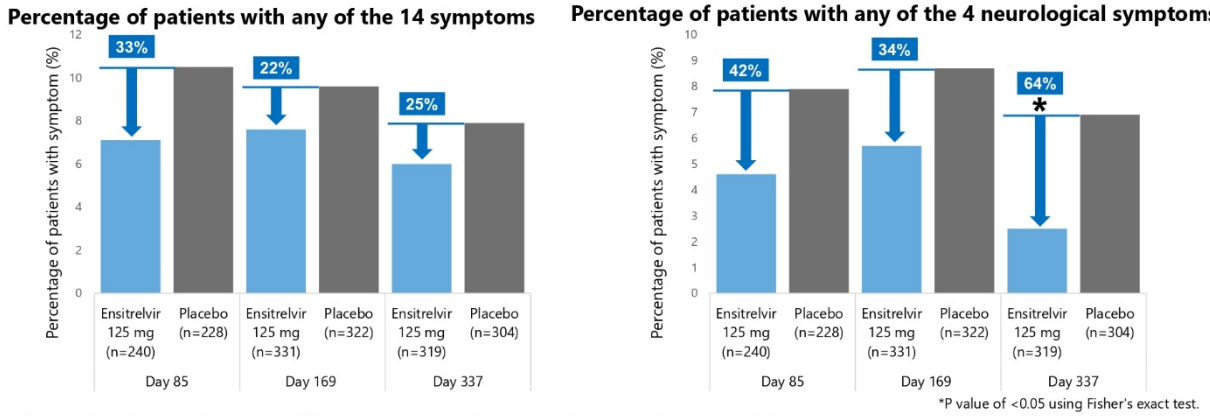
This time, we have revised the definition of Long COVID, analysing it from a different angle as well.

Again, in the CROI, and in the pre-revision results I showed you earlier, the definition is based on patient who has at least one symptom that is more than mild symptoms and considered it is related to COVID-19. So, what we have revised it with this time, is that at least one mild or greater symptom remains the same. In addition, we will show the results of the Long COVID analysis for those who responded that they have not returned to the state of health to pre-COVID level.

Proportion of Patients with Long COVID Symptoms and Effect on Long COVID Symptoms

Definition of Long COVID symptoms: Specified symptom in patients who answered "not returned to pre-COVID health"



- **Even with the revised definition, the proportion of patients with Long COVID symptoms in the ensitrelvir 125 mg was lower than that in the placebo group at all timepoints.**
- **64% reduction in the proportion of patients presenting with the four most commonly reported post-acute neurological symptoms on Day 337**

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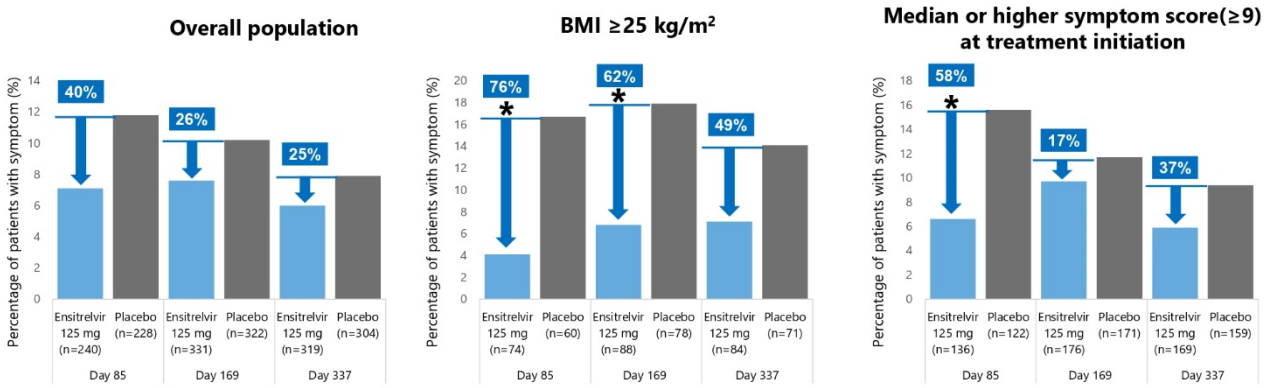
The left graph shows data for 14 symptoms. The right graph shows data for 4 symptoms. The results of the various analyses are not very different, but the frequency of placebo and the reduction in risk with the actual drug were consistent across all 14 symptoms and post-COVID-19 neurological symptoms at all time points.

Proportion of Patients with Long COVID Symptoms and Effect on Long COVID Symptoms (Patients with any of the 27 symptoms of COVID-19)



- **On Day 337, 25% reduction in the proportion of patients with any of the 27 symptoms characteristic of COVID-19**
- **Greater risk reduction was observed in patients who with BMI ≥25 kg/m2 and patients with median or higher symptom score at the start of treatment**
  - **On Day 337, BMI ≥25 kg/m2; 49%, patients with median or higher symptom score at treatment initiation; 37%**

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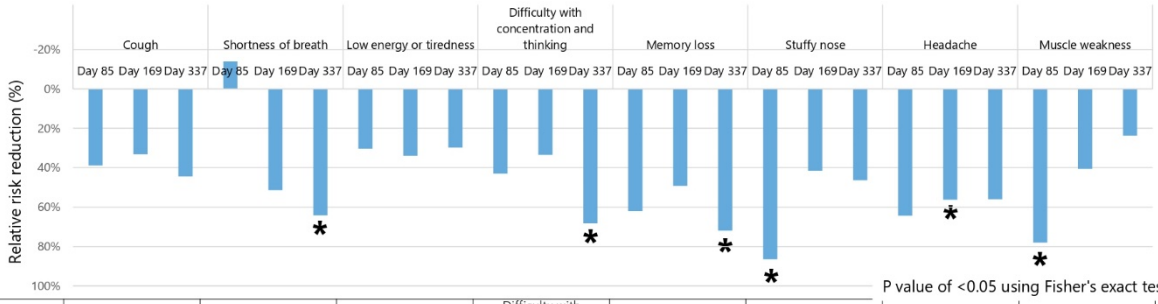
In addition, as I have just shown you 14 symptoms and 4 typical neurological symptoms, the survey itself has 27 COVID-19 symptoms, which is a very wide variety of symptoms. Therefore, even if we aggregate all the data for patients with all 27 symptoms or 1 of the 27 symptoms, we still find that the risk is reduced in this way.

The analysis of subgroups revealed that the risk of Long COVID was slightly increased in patients with BMI of 25 or more, which would be considered moderately obese, and in patients with 14 baseline symptoms, specifically those with relatively strong acute symptoms before receiving the medication. The results of the new additional analysis showed that the risk of Long COVID was slightly increased in such patients, and that the effect of the treatment was very pronounced.

Effect on Long COVID Symptoms（overall population, individual symptom reported (≥5%)[a])



	Cough			Shortness of breath			Low energy or tiredness			Difficulty with concentration and thinking			Memory loss			Stuffy nose			Headache			Muscle weakness		
	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337
125mg	9/240	11/331	7/319	6/240	9/331	6/319	11/240	19/331	14/319	9/240	13/331	6/319	4/240	12/331	5/319	1/240	9/331	9/319	3/240	9/331	6/319	3/240	11/331	8/319
placebo	14/228	16/322	12/304	5/228	18/322	16/304	15/228	28/322	19/304	15/228	19/322	18/304	10/228	23/322	17/304	7/228	15/322	16/304	8/228	20/322	13/304	13/228	18/322	10/304

- **On Day 337, a statistically significant reduction in the risk of developing shortness of breath and cognitive symptoms (difficulty with concentration and thinking; memory loss) with ensitrelvir treatment was observed at some time points.**
- **On Day 337, reduction in shortness of breath: 64%, difficulty with concentration and thinking: 68%, memory loss: 72%**

[a] Long COVID symptoms seen in placebo group and at any time point with an incidence of ≥5% were shown

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And here are all the symptoms, shown one by one in the breakdown.

Due to the convenience of the slides, we have only picked up representative symptoms, specifically those that occurred in more than 5% of patients on placebo.

As you can see, the risk of cough, shortness of breath, low energy, and various central nervous system symptoms was reduced by taking the medication for the patients with persistent symptoms or with complaints of central nervous system dysfunction after the acute phase. The results of the one-year follow-up study suggests that the risk was reduced by taking the medication.

Summary

- **Ensitrelvir treatment reduced the risk of developing Long COVID by 25% at follow-up one year after infection**
- **In particular, the risk was significantly reduced for symptoms such as shortness of breath (64%), decreased concentration and thinking (68%), and memory loss (72%)**
- **The Long COVID risk reduction by ensitrelvir was greater in patients with BMI ≥25 kg/m² or severe post-infection symptoms, with risk reductions of 49% and 37%, respectively**

- **The results indicate that early treatment of COVID-19 with ensitrelvir may reduce the risk of a number of symptoms associated with Long COVID over a long period of time (one year)**

- **Further research will be conducted in the Global Phase 3 Trial (SCORPIO-HR)**

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Here is a summary.

Ensitrelvir treatment reduced the risk of developing Long COVID by 25% at follow-up one year after infection. In particular, the risk was significantly reduced for symptoms such as shortness of breath, decreased concentration and thinking, and memory loss in percentage term as you can see. The results were summarized as 49% and 37% reduction in risk for patients with high BMI and strong symptoms, respectively.

These results suggest the possibility of reducing the risk of developing Long COVID over a very long period of time.

Incidentally, we have been presenting the results based on this exploratory analysis, and we are now accumulating data to obtain more reliable evidence in the global Phase III study that is currently underway.

Question & Answer

Kyokawa: Thank you very much. We will now move on to the question & answer session.

Now, Mr. Sakai of Credit Suisse Securities, please ask your questions.

Sakai: This is Sakai of Credit Suisse. Thank you very much for the explanation today.

I would like to ask, and this may be a different question from the results of this study, but I think there was a theory that COVID-19 has a place to stay in the body of infected patients, or maybe for virus itself, and it causes Long COVID, or prolonged infection symptoms rebound. Based on your clinical experiences, I wonder if this theory is not too close but not too far.

I wonder if it is true that this virus has such a character that hangout in a place in the infected body, or it is called as reservoir over there. I would like to ask first in this area.

Also, this question is for Mr. Uehara that the results of this study have confirmed the efficacy of ensitrelvir on Long COVID, but what do you think about the risk or possibility that the virus will do something bad again in the future?

Please tell me about these two.

Yamato: Thank you very much. Let me begin, Yamato.

Exactly as you have just said, the fact that the virus has not been firmly knocked out of the body, especially in immunocompromised patients, may lead to reproduction of severe disease and Long COVID. There is a strong theory that persistent infection is the cause of such diseases. Also, from the data I have shown today in my daily clinical practice, the virus remains in the body and rises when the body's immune system is insufficient in some way.

In the actual clinical setting, I believe that using ensitrelvir to help eliminate the virus completely will be effective in preventing severe recurrence and Long COVID. Thank you very much.

Uehara: Thank you very much. I also have the same feeling that the ensitrelvir itself is a drug that prevents the virus from spreading in the upper respiratory tract and lurking in the reservoir, and it strikes the increasing virus in the upper respiratory tract as early as possible. If this could be accomplished, symptoms would improve faster and the number of patients with persistent symptoms would be reduced.

To be honest, we do not know if the virus is actually present in the reservoirs of all patients with Long COVID, but even if the virus is not present in the reservoirs, the spread of the virus can trigger various inflammatory responses throughout the body, which can persist as symptoms for a long time. Basically, the disease is caused by viral infection, and we believe that antiviral drugs play a very important role in suppressing viral proliferation and inflammation at an early stage.

Sakai: I understand. Thank you very much.

Kyokawa: Next, Mr. Ueda from Goldman Sachs, please.

Ueda: My name is Ueda from Goldman Sachs. I would like to ask you one thing about how to look at the data in this Phase III part. Regarding the long-term data for Long COVID, I was wondering if there is a difference

between those who are responding to some extent and those who remain symptomatic for a long period of time. If you have any thoughts on why there is a difference, please let me know.

And you also explained that the three symptoms, shortness of breath, poor concentration and thinking, and memory loss, were particularly effective. Can you tell us what you think about the particular effect you are seeing on these symptoms?

Uehara: Thank you very much. As for your second question, although I have selected only the most representative symptoms, all of symptoms are generally improve.

If we include items that are less than 5% of the total that the frequency is too little, it will show another way, so we are presenting representative items for visual purposes, but overall, they are in improvement trend.

In fact, we are analyzing various angles this time, and specifically, symptoms that are present at one month are still present at another three months. Even if we analyze the data from the perspective of persistence in this manner, for example symptoms remains at three months and six months, the risk is still decreasing.

Even if we do not consider the persistence of the disease, the overall risk has decreased even if we count the number of patients who have returned to normal at each point in time. There are certain patients who have always been at risk, and there are new patients who have developed symptoms that cause problems at a later point in time, so it is not that only certain patients have been at risk for a long time, or have had symptoms for a long time, and not lowering the risk for them all the time.

Ueda: Thank you very much. The second question is also about the trial. I was wondering if you have done any analysis to see if the effect on Long COVID differs depending on the timing of administration.

I think you administered the drug within 120 hours, but if you have any suggestions, for example, if it would be more effective if administered earlier. Could you tell us about it?

Uehara: As you mentioned, the results of this trial were compiled from the data of patients who took the drug within a total of 120 hours, or five days.

We have 300 and more responses from a very large number of patients but to be honest, it is difficult to read the data clearly, because the sample size is inevitably smaller when we further break it down into sub-patient demographics.

Specifically, I expect that the reduction in risk will be more pronounced if the drug is taken within 48 or 72 hours, however there are no characteristics observed that it would be dramatically improved if the drug is taken within 72 hours.

Ueda: Okay, thank you. That is all from me. Thank you very much.

Kyokawa: Mr. Tsuzuki of Mizuho Securities, please.

Tsuzuki: Thank you for your explanation. My name is Tsuzuki of Mizuho Securities. I would like to ask one point to Dr. Yamato, and one point to Mr. Uehara.

First of all, I would like to ask Dr. Yamato. Since I believe that the data presented here is what is called a retrospective review, I would like to ask from your sense of clinical practice, what is the most likely course of the disease if the patient had been given remdesivir without changing to ensitrelvir, which in the actual trial patients did not see improvement with remdesivir and changed to ensitrelvir. If you have anything to show us in terms of your sense of clinical practice, I would be very interested to hear.

Yamato: Thank you very much. First of all, remdesivir is a very good drug. I believe it is used in Japan as first line in hospitalized patients, as well as in the guidelines in the US. However, the current situation with various mutant strains, such as Omicron, is that the rebound phenomenon or symptoms are not improving.

Then the patients and we are afraid that they might develop pneumonia in the future, and also the patients have many complications. Especially for patients with malignant tumors and hematological diseases are especially susceptible to pneumonia, so we have to stop treatment temporarily once the virus is not cured or the patients are not healed from COVID-19.

Even if the patient does not develop pneumonia from COVID-19, the delay in the original treatment may have a negative impact on the prognosis of the total patient's life. In such a situation, we believe that switching to ensitrelvir and bring virus to negative at early stage can be a great weapon as it enables us to treat the underlying disease sooner.

Tsuzuki: Thank you very much. I would like to add one more point. In that sense, it has been quite some time since the emergency approval, and I am wondering if you have seen any improvement in the prescribing rate in your sense of clinical practice, either in this data or in the data from the Long COVID. I would appreciate it if you could give me a sense of the clinic scene in this area.

Yamato: Thank you very much. We look at this and confirm it can bring the negative viral titer fairly quickly. We are actually using ensitrelvir at the first timing in our hospital, and the bed turnover is very good, and the patients get well quickly. Viral titers also become negative.

In other words, I strongly believe, not only myself but also our staff and patients, that this drug is making a great contribution to the improvement of the medical shortage due to the ninth wave. This is my honest opinion in my clinical field. Thank you very much.

Tsuzuki: Thank you very much. Then I wanted to ask Mr. Uehara a few questions. I would like to ask you a few questions from the perspective of how to read the data. At this point in time, in the Long COVID section, you have presented data assets for Day 85, Day 169, and Day 337, where the number of "n" has increased considerably to 314. I would like to know your perspective on how we should read this point.

Uehara: Let me explain on slide p17 of the briefing session. this slide shows the number of patients who responded at time of Day 85 and the number of patients who responded at time of Day 169, respectively. The denominator number of patients who responded at each point of time is slightly difference because all of patients did not respond 100% at all of points of time.

The number of "n" in the patient demographic that I showed at very beginning, is the number who responded at least at some point in time, and is 341 and 333 in total. The number of "n" broken down to each point in time is the result of each tally.

Tsuzuki: I understand. I think these perspectives are on Long COVID data, and this is just a follow-up after emergency approval. I wonder when much larger data will be published or will be reviewed in paper? Or should we wait for the SCORPIO-HR, global Phase III? I am interested to know your perspective on this. This is question about the timing of the next data publishing.

Uehara: First of all, now that we have all the final results, we are in the process of preparing paper to be submitted to an international journal.

Furthermore, we are using the same questionnaire to compile data in the global SCORPIO-HR trial. The SCORPIO-SR trial, the one I just presented, is an exploratory analysis, which is how we can see the effect of the drug. Long COVID is a new perspective, so there is no internationally established evaluation method.

Therefore, we have been able to confirm in this trial that we can open up this area, or rather, we can see the effects on patients by conducting this kind of analysis. The SCORPIO-HR trial is being conducted in a manner that pre-specifies and verifies this.

Tsuzuki: I understand. That is all from me. Thank you very much.

Kyokawa: Thank you very much. Next, Mr. Hashiguchi of Daiwa Securities. Please ask your questions.

Hashiguchi: My name is Hashiguchi, Daiwa Securities. I have a question for Dr. Yamato.

If the patients in this trial, those who did not show sufficient antiviral efficacy with remdesivir, but were not switched to ensitrelvir treatment, what would be the usual results of treatment? Since there is no control group, I am not sure how much of this progress is due to the effect of ensitrelvir. I would like to ask you in this regard.

And one more point, this time ensitrelvir is given after remdesivir, but what do you think would happen if remdesivir is given to a person whose sufficient antiviral effect was not confirmed with ensitrelvir?

Does this result mean that the sensitivity to antiviral drugs varies from patient to patient, and that if one drug failed, another drug was tried and found to be effective, or does it mean that the antiviral effect differs from drug to drug? I would like to understand the significance of giving treatment in this order.

Yamato: Thank you very much. As I partially answered earlier, regarding which antiviral drug should be used in the first line for critically ill patients who are hospitalized, there has been no mention of this in the Japanese guidelines, but the NIH guidelines in the US, it states that remdesivir should be used in the first line for hospitalized patients.

Therefore, as written in the guidelines, drugs show evidence should be used in first place in Japan, so we administered remdesivir accordingly.

But for elderly patients, especially those on dialysis, those with renal failure, or malignant tumors. Then, for immunosuppressed patients, especially those who are immunocompromised, it is difficult to bring the virus to negative status with the existing antiviral drugs available so far. Or it will rebound. This has been reported from various sources. There is a case in our hospital where we have used it for 22 days, in the case I mentioned earlier, and even if we use it for more than 10 days or use it beyond the indication, it is not easy to see a negative viral titer.

This would lead to a more prolonged spread of the virus in immunocompromised patients or even resistance to the virus. Or there is a possibility that such virus could spread to others. Another issue is the inability to treat the original and primary disease. Alternatively, it is presumed that COVID-19 pneumonia may occur when the virus remains for a long period of time and multiplies more strongly in the lungs, leading to progression of COVID-19 pneumonia.

Ensitrelvir is 3CL protease like nirmatrelvir/ritonavir, and the mechanism of action is probably the same, but the main feature of ensitrelvir is that it can be used even in patients with kidney problems. We also use it for our dialysis patients. I think that is one of the advantages.

The other thing is, of course, that there are individual differences when we see why the virus does not disappear easily. The strength of the patient's immune system, rather than mutation of virus to resistant strain, which is a particularly and largely different by individual. In other words, the patients on the drug have very weak immune systems, and only one drug, especially remdesivir, works to inhibit RNA synthesis. So even if a drug with a different mechanism from 3CL protease does not work well, 3CL protease may work well, and vice versa.

For example, as I introduced a little earlier, there are a few, but a small number, that show rebound in viral dose after switching to ensitrelvir. However, it does not really rebound to the maximum range and I think the improvement of symptoms is not directly related to it in some aspects.

However, while following the existing guidelines, we have found that ensitrelvir can be used in patients with high risk factors for severe disease in the form of switching drug and we are currently accumulating more data. We have realized that by using ensitrelvir from the initial stage, we can achieve very effective clinical results with only one drug for five days of administration. Also, we can achieve negative viral titers or even negative viral titers at an early stage with quantitative antigen level.

In other words, we are aware that this drug has the strongest antiviral action compared to other drugs, and we are using it in a variety of patients. That is our honest feeling. Thank you very much.

Hashiguchi: Thank you. Also, just one more question for Mr. Uehara, when do you expect to publish the results of the SCORPIO-HR study, the global Phase III study that was introduced at the end?

Uehara: The accumulation of cases is almost complete, and since Long COVID requires an additional three months, we are considering the possibility of publishing some results by the end of this fiscal year or a little after that.

Hashiguchi: When you said the end of this fiscal year, do you mean that for Long COVID data, and the primary endpoints may be published a little earlier?

Uehara: We are still discussing with the authorities when to make the key break there. In the actual verification of Long COVID, there is a possibility that the authorities will request us to wait three months without breaking the key. I hope you will forgive me for saying that this area is still under ongoing discussion.

Hashiguchi: I understand. Thank you very much, that is all.

Kyokawa: Thank you very much. We will conclude the meeting.

Thank you all very much for taking time out of your busy schedules to join us today.

[END]