Summary of Clinical Study Results for General Audience
Plain Language Summary

1. STUDY NAME

A Phase 2/3 Study of S-217622 in Participants Infected with SARS-CoV-2 (Study 2108T1221)

2. WHO SPONSORED THIS STUDY?

This study was sponsored by Shionogi & Co., Ltd.

3. GENERAL INFORMATION ABOUT THIS STUDY

Coronavirus disease 2019 (COVID-19) is an infection caused by the coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

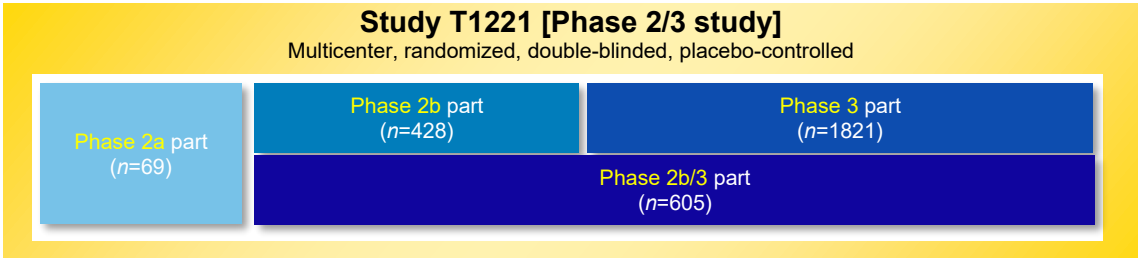
Symptoms often seen in cases of COVID-19 include fever, cough, runny nose, blocked nose, throat pain, muscle pain, and diarrhea, which are similar to common cold symptoms. In addition, other symptoms including loss of taste and sense of smell have been reported. In particular, high-risk patients with advanced age, cardiovascular disease, respiratory disease, renal disease, diabetes mellitus, obesity, or immunodeficiency are more likely to experience severe conditions. Such patients experience rapidly progressing pneumonia, resulting in shortness of breath, dyspnea, etc., and may require treatments with oxygen inhalation, ventilator, or extracorporeal membrane oxygenation (ECMO). This led to the severe tightening and collapse of healthcare systems worldwide during the initial stage of the pandemic.

Xocova (generic name: ensitrelvir, development phase name: S-217622) prevents the growth of the virus in the body by stopping the activity of an enzyme called protease that is required for the virus to grow. This means that it is expected to shorten the time until symptoms disappear (the time until the patient returns to the condition before symptoms appeared).

This Study T1221 was done to find out the effect (efficacy) and safety in patients taking Xocova tablets compared with patients taking placebo tablets (a dummy drug that looks like Xocova tablets but does not contain active drug ingredients of Xocova tablets) (Figure 1).

This was a “double-blinded” study. That means that neither the patients nor the study doctors knew who took Xocova tablets and who took placebo tablets during this study. Using a placebo helps make study results unbiased and fair. Patients in this study were randomly assigned to one of these groups to reduce bias between the groups.

Figure 1 Summary and Structure of the Study T1221



A phase 2 study is done to find out how the study drug was effective and safe, and to determine how to use the study drug. In a phase 2 study, a new treatment is given generally to a small number of patients. A phase 3 study is done to find out how the study drug was effective and safe, and to determine finally how to use the study drug standardly. In a phase 3 study, a new treatment is done generally in a large number of patients.

This Study T1221 is a single phase 2/3 study, but it is divided into the following 4 parts, each with different patients and different purposes (Table 1). In the **phase 2a part**, the antiviral effect was checked exploratively in patients with mild/moderate or asymptomatic (without any symptoms) SARS-CoV-2 infection. In the **phase 2b part**, the early improvement effect on clinical symptoms and the early antiviral effect were checked in patients with mild or moderate SARS-CoV-2 infection. In the **phase 3 part**, the effect of improving clinical symptoms was verified in patients with mild or moderate SARS-CoV-2 infection. In the **phase 2b/3 part**, the effect of preventing the occurrence or worsening of symptoms was explored in patients with asymptomatic SARS-CoV-2 infection or SARS-CoV-2 infection with mild symptoms only.

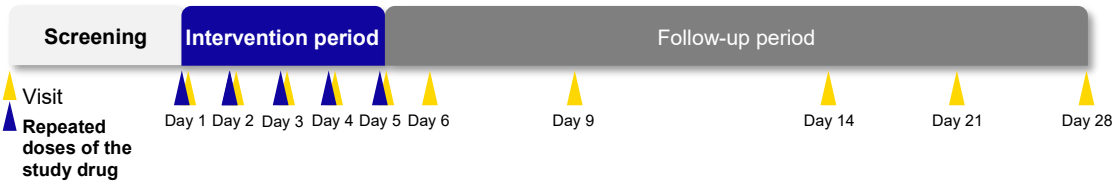
Table 1 Patients and Purpose in Each Part

	Phase 2a part	Phase 2b part	Phase 3 part	Phase 2b/3 part
Patients	Patients with mild/moderate or asymptomatic SARS-CoV-2 infection	Patients with mild/moderate SARS-CoV-2 infection	Patients with mild/moderate SARS-CoV-2 infection	Patients with asymptomatic SARS-CoV-2 infection/SARS-CoV-2 infection with mild symptoms only
Purpose	Exploratively checking the antiviral effect	Checking the early improvement effect on clinical symptoms and the early antiviral effect	Verifying the effect of improving clinical symptoms	Exploring the effect of preventing the occurrence or worsening of symptoms

An overview of the study schedule is shown in Figure 2.

The study was divided into an intervention period in which participants took the study drug (days 1 to 5) and the follow-up period in which the health status of participants was checked (days 6 to 28), and each of the four parts was conducted according to the same schedule.

Figure 2 Overview of Schedule



The study drugs used in this study were Xocova tablets and placebo tablets. Each Xocova tablet contained 125 mg or 250 mg of the active ingredient (ensitrelvir). Placebo tablets look the same as Xocova tablets but do not contain the active ingredient. In the intervention period, as shown in Table 2, patients were randomly divided into groups and took Xocova tablets or placebo tablets.

Table 2 Dosage and Method of Taking Xocova Tablets or Placebo Tablets

Group	Dose (active ingredient)	
	Date of first dose	Days 2 to 5 of dosing
Xocova tablets 375/125 mg	375 mg	125 mg
Xocova tablets 750/250 mg	750 mg	250 mg
Placebo tablets	---	---

This study was done in 4 countries, including Japan (the countries in the study were different in each part). It started in September 2021 and ended in August 2022.

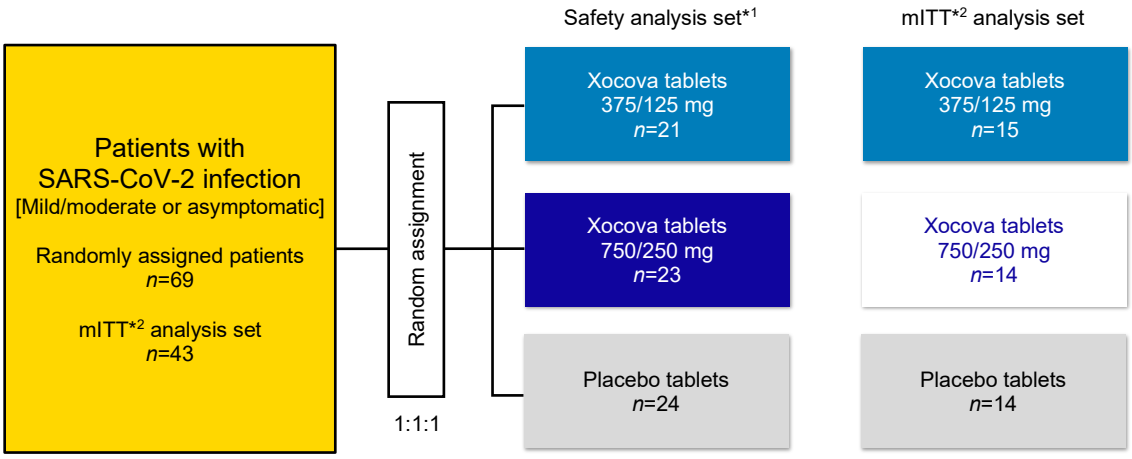
3.1 Phase 2a part

This phase 2a part was done to exploratorily check the antiviral effect in patients with mild/moderate or asymptomatic (without any symptoms) SARS-CoV-2 infection.

Antiviral effect	The change in virus titer (the amount of infectious virus) after taking Xocova tablets compared with directly before taking Xocova tablets

An overview of the phase 2a part is shown in Figure 3.

Figure 3 Overview of the Phase 2a Part



mITT = modified intention-to-treat; RT-PCR = reverse transcription polymerase chain reaction
*1 All patients who took the study drug at least once.
*2 mITT analysis set. All patients who were randomly assigned to the study drug, and who were confirmed to have SARS-CoV-2 infection based on the results of RT-PCR before they received the drug, and who had a SARS-CoV-2 virus titer detected at baseline.

3.1.1 Included patients

Patients with mild/moderate or asymptomatic SARS-CoV-2 infection participated in this part. This part was done in Japan only.

Of the 69 patients with mild/moderate or asymptomatic SARS-CoV-2 infection participating in this part, 65 patients completed this part, and 43 patients were included in analysis of the primary efficacy endpoint (these patients were the mITT analysis set), and of these, 15 patients were in the 375/125 mg group, 14 patients were in the 750/250 mg group and 14 patients were in the placebo group. Of the 69 patients participating in this part, 4 patients (375/125 mg group: 1 patient, 750/250 mg group: 0 patients, placebo group: 3 patients) had their participation in this part stopped, and did not participate up to the end of the part. The main reason for stopping participation was the request of the patient (in 3 patients).

3.1.2 General results

The mean (and standard deviation) change in SARS-CoV-2 virus titer* compared to just before taking the drug ($\log_{10}$ [$TCID_{50}$/mL]) was −1.05 (1.17) in the 375/125 mg group, −2.03 (1.21) in the 750/250 mg group and −0.86 (0.93) in the placebo group (and the results for each group are in the same order below) on day 2, −2.42 (1.42), −2.81 (1.21) and −1.54 (0.74) on day 4 and −2.56 (1.35), −2.76 (1.19) and −2.08 (0.91) on day 6. Compared to the placebo group, the titer had decreased by approximately 1 $\log_{10}$ ($TCID_{50}$/mL) in the 750/250 mg group on day 2 and by approximately 1 $\log_{10}$ ($TCID_{50}$/mL) in each of the 375/125 mg group and the 750/250 mg group on day 4. Compared to the placebo group, there was a statistically significant decrease in the 750/250 mg group for day 2 and for day 4 ($p = 0.0212$ and $p = 0.0083$, respectively).

* Amount of virus (titer) that kills 50% of tissue culture cells in 1 mL

3.1.3 What were the side effects?

A lot of research, especially side effects, is needed to know whether a drug causes medical problems.

- A “side effect” (unwanted effects) means any medical problem that is judged by the study doctor to be caused by a study drug used in the study.
- A “serious side effect” means a side effect that is considered “serious” when it results in death, is life-threatening, causes lasting problems, needs hospital care, causes birth problems or is other important state.

In this part, no patients experienced serious side effects, died during the study or experienced side effects leading to Xocova tablets being stopped.

The overall incidence of side effects in patients with mild/moderate and asymptomatic SARS-CoV-2 infection was 23.8% in the 375/125 mg group, 43.5% in the 750/250 mg group and 0% in the placebo group. The only side effect reported in 3 or more patients in the groups taking Xocova tablets was decreased high density lipoprotein, which occurred in 14.3% of patients in the 375/125 mg group and 34.8% of patients in the 750/250 mg group.

Throughout the phase 2a part, no major problems with the safety of Xocova tablets were found.

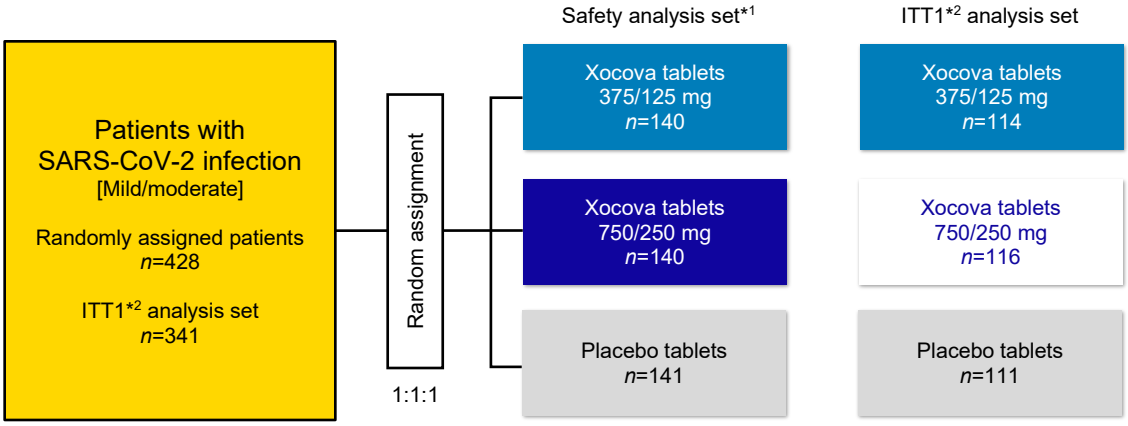
3.2 Phase 2b part

This phase 2b part was done to check the early improvement effect on clinical symptoms and the early antiviral effect in patients with mild or moderate SARS-CoV-2 infection.

Early improvement effect on clinical symptoms	Change per unit time in 12 symptoms of COVID-19 (malaise [feeling fatigued], myalgia [muscle pain] or body pain, headache, chills or sweating, feeling feverish or pyrexia [fever], runny nose or blocked nose, throat pain, cough, shortness of breath [dyspnea], feeling queasy, vomiting, diarrhea) up to day 6 after starting Xocova tablets
Early antiviral effect	The change in virus titer (the amount of infectious virus) on day 4 after starting Xocova tablets compared with directly before taking Xocova tablets

An overview of the phase 2b part is shown in Figure 4.

Figure 4 Overview of the Phase 2b Part



ITT1 = intention-to-treat 1
*1 All patients who took the study drug at least once.
*2 ITT1 analysis set. All patients who were randomly assigned to the study drug and who had a SARS-CoV-2 virus titer detected at baseline.

3.2.1 Included patients

Patients with mild or moderate SARS-CoV-2 infection participated in this part. This part was done in Japan and South Korea.

Of the 428 patients with mild or moderate SARS-CoV-2 infection who participated in this part, 409 patients completed this part, 341 patients (199 male patients, 142 female patients, ages: 12 years to 69 years) were included in efficacy evaluation (these patients were the ITT1 analysis set), and of these, 114 patients were in the 375/125 mg group, 116 patients were in the 750/250 mg group and 111 patients were in the placebo group. Of the 428 patients who participated in this part, 19 patients (375/125 mg group: 8 patients, 750/250 mg group: 7 patients, placebo group: 4 patients) had their participation in this part stopped and did not participate up to the end of the part. The main reason for stopping participation was the request of the patient (in 11 patients).

3.2.2 General results

The mean (and standard deviation) amount of change per unit time in the total score for the 12 symptoms of SARS-CoV-2 infection up to 120 hours after the start of the drug (day 6) was −5.95 (4.02) in the 375/125 mg group, −5.42 (3.70) in the 750/250 mg group and −4.92 (3.25) in the placebo group. There was no statistically significant difference from the placebo group in either the 375/125 mg group or the 750/250 mg group.

However, the mean (and standard deviation) amount of change (log_{10} [$TCID_{50}$/mL]) in the SARS-CoV-2 virus titer on day 4 compared to directly before taking the drug was −1.69 (0.84) in the 375/125 mg group, −1.43 (0.83) in the 750/250 mg group and −1.06 (0.99) in the placebo group. The adjusted estimate for the amount of change in the SARS-CoV-2 virus titer on day 4 compared to just before taking the drug showed a decrease of 0.41 log_{10} ($TCID_{50}$/mL) for each of the 375/125 mg group and

750/250 mg group compared to the placebo group, and a statistically significant difference from the placebo group was shown in both groups ($p < 0.0001$ and $p < 0.0001$, respectively).

3.2.3 What were the side effects?

To evaluate early safety in this part, unblinding* was done when the observation on day 6 had been completed in the last patient, and the safety was evaluated based on the results collected up to the unblinding. These results are shown below.

* Unblinding means telling the study doctor and the patients participating in the study which treatment each individual patient received (Xocova tablets or placebo tablets).

No patients experienced serious side effects or died during the study.

The number of patients who experienced side effects leading to the drug being stopped was 2 in the 375/125 mg group (eczema in 1 patient and nausea/headache in 1 patient), but later, these side effects resolved.

The incidence of side effects in patients with mild or moderate SARS-CoV-2 infection was 9.3% in the 375/125 mg group, 18.6% in the 750/250 mg group and 5.0% in the placebo group.

The only side effect with an incidence of 2% or more was decreased high density lipoprotein in the groups taking Xocova tablets, and these incidences were 5.7% in the 375/125 mg group and 12.1% in the 750/250 mg group.

Compared with the results up to unblinding explained above, the incidence of side effects up to day 28 was slightly higher, but it appeared that there was almost no change in the safety of Xocova tablets.

Throughout the phase 2b part, no major problems with the safety of Xocova tablets were found.

3.3 Phase 3 part

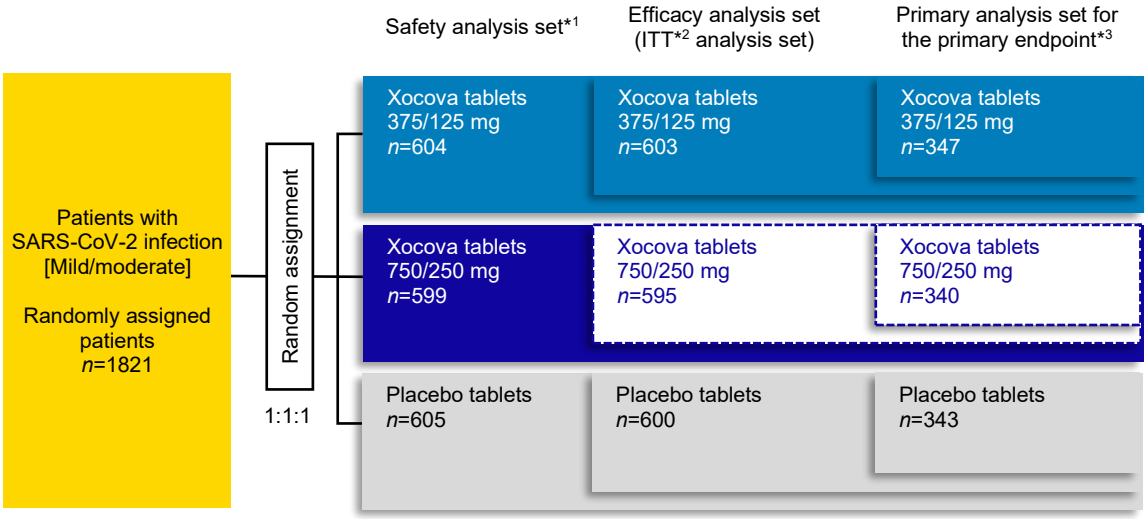
This phase 3 part was done to verify the effect of improving clinical symptoms in patients with mild or moderate SARS-CoV-2 infection.

Effect improving clinical symptoms	The period of time from the start of taking Xocova tablets until the 5 symptoms of COVID-19 (runny nose or blocked nose, throat pain, cough, feeling feverish or pyrexia [fever], malaise [feeling fatigued]) resolved*.

* Disappearance of symptoms (returning to the state before the onset of disease)

An overview of the phase 3 part is shown in Figure 5.

Figure 5 Overview of the Phase 3 Part



ITTI = intention-to-treat
*1 All patients who took the study drug at least once.
*2 ITT analysis set. All patients who were randomly assigned within 120 hours after the onset of COVID-19 and who were confirmed to have SARS-CoV-2 infection based on the results of RT-PCR.
*3 All patients in the ITT analysis set who were randomly assigned in less than 72 hours after the onset of COVID-19.

3.3.1 Included patients

Patients with mild or moderate SARS-CoV-2 infection participated in this part. The patients in this part were from Japan, South Korea and Vietnam.

Of the 1821 patients with mild or moderate SARS-CoV-2 infection who participated in this part, 1769 patients completed this part, 1798 patients were included in efficacy analysis (these patients were the ITT analysis set), 1030 patients (552 male patients, 478 female patients, ages: 12 years to 68 years) were included in analysis of the primary endpoint (these were the patients included in efficacy analysis who were randomly assigned in less than 72 hours after the onset of COVID-19), and of these, 347 patients were in the 375/125 mg group, 340 patients were in the 750/250 mg group and 343 patients were in the placebo group. Of the 1821 patients who participated in this part, 52 patients (375/125 mg group: 11 patients, 750/250 mg group: 21 patients, placebo group: 20 patients) had their participation in this part stopped and did not participate up to the end of the part. The main reason for stopping participation was the request of the patient (in 24 patients).

3.3.2 General results

In primary analysis on effect improving clinical symptoms (5 symptoms), there was a statistically significant difference between the 375 mg/125 mg Xocova tablets group and the placebo group ($p = 0.04$, generalized Wilcoxon test). This verified the efficacy of Xocova tablets in patients with mild or moderate SARS-CoV-2 infection in the 375/125 mg group.

Of the patients included in efficacy analysis, 1030 patients were randomly assigned in less than 72 hours after the onset of COVID-19 and the time until the 5 symptoms of COVID-19 resolved in a half of the patients in each group was shorter by 24.3 hours (about 1 day) in the 375/125 mg group compared with the placebo group. The time to resolution in the 750/250 mg group was shorter by 21.0 hours (just under 1 day) compared with the placebo group (Table 3).

Table 3 Efficacy (Primary Analysis) Results in the Phase 3 Part

	Group		
	375/125 mg	750/250 mg	Placebo
Number of patients	347	340	343
Time until symptoms resolved*	167.9 hours	171.2 hours	192.2 hours
Difference from placebo	−24.3 hours	−21.0 hours	—

* The time until the 5 symptoms of COVID-19 resolved in half of patients

3.3.3 What were the side effects?

In this part, no patients experienced serious side effects or died during the study.

The number of patients who experienced side effects leading to the drug being stopped was 2 in the 375/125 mg group (eczema in 1 patient and vomiting in 1 patient) and 2 in the 750/250 mg group (rash), but later, these side effects resolved or were resolving.

The incidence of side effects in the patients with mild or moderate SARS-CoV-2 infection were 24.5% in the 375/125 mg group, 36.2% in the 750/250 mg group and 9.9% in the placebo group.

The side effects with incidences of 2% or more were decreased high density lipoprotein with an incidence of 18.4%, increased blood bilirubin with an incidence of 2.8% and increased blood triglycerides with an incidence of 2.6% in the 375/125 mg group, decreased high density lipoprotein with an incidence of 26.2%, increased blood triglycerides with an incidence of 6.2%, increased blood bilirubin with an incidence of 5.8%, headache with an incidence of 2.2%, and decreased blood cholesterol with an incidence of 2.0% in the 750/250 mg group, and increased blood triglycerides only with an incidence of 2.8% in the placebo group.

Throughout the phase 3 part, no major problems with the safety of Xocova tablets were found.

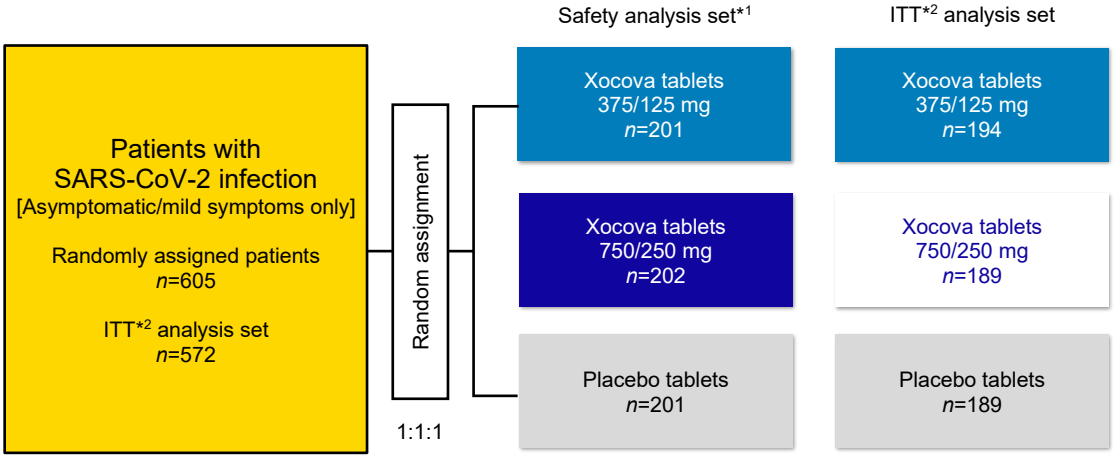
3.4 Phase 2b/3 part

This phase 2b/3 part explored the effect of preventing the occurrence or worsening of symptoms in patients with asymptomatic SARS-CoV-2 infection or SARS-CoV-2 infection with mild symptoms only.

Effect preventing occurrence of symptoms	The proportion of asymptomatic patients who were found to have developed the COVID-19 symptoms or pyrexia (fever) after taking Xocova tablets
Effect preventing worsening of symptoms	The proportion of patients with infection with mild symptoms only whose COVID-19 symptoms or pyrexia (fever) were found to have worsened after taking Xocova tablets

An overview of the phase 2b/3 part is shown in Figure 6.

Figure 6 Overview of the Phase 2b/3 Part



ITT = intention-to-treat
*1 All patients who took the study drug at least once.
*2 ITT analysis set. All patients who were randomly assigned to the study drug and who were confirmed to have SARS-CoV-2 infection based on the results of RT-PCR.

3.4.1 Included patients

Patients with asymptomatic SARS-CoV-2 infection or SARS-CoV-2 infection with mild symptoms only participated in this part. The patients in this part were from Japan, South Korea and Vietnam.

Of the 605 patients with asymptomatic SARS-CoV-2 infection or SARS-CoV-2 infection with mild symptoms only who participated in this part, 585 patients completed this part, 572 patients (322 male patients, 250 female patients, ages: 12 years to 69 years) were included in efficacy analysis (these patients were the ITT

analysis set), and of these patients, 70 patients (375/125 mg group: 23 patients, 750/250 mg group: 25 patients, placebo group: 22 patients) had asymptomatic SARS-CoV-2 infection and 502 patients (375/125 mg group: 171 patients, 750/250 mg group: 164 patients, placebo group: 167 patients) had SARS-CoV-2 infection with mild symptoms only. Of the 605 patients who participated in this part, 20 patients (375/125 mg group: 6 patients, 750/250 mg group: 6 patients, placebo group: 8 patients) had their participation in this part stopped, and did not participate up to the end of the part. The main reason for stopping participation was the request of the patient (in 13 patients).

3.4.2 General results

The effect of preventing the occurrence of COVID-19 symptoms was evaluated in patients with asymptomatic SARS-CoV-2 infection. The proportion of patients who were found to have developed 8 symptoms of COVID-19 (runny nose or blocked nose, throat pain, cough, malaise [feeling fatigued], feeling feverish or pyrexia [fever], shortness of breath [dyspnea], taste abnormality and dysosmia [smell abnormality]) or pyrexia (fever) according to temperature assessment by day 10 of taking the drug was 4.3% (1/23 patients) in the 375/125 mg group, 20.0% (5/25 patients) in the 750/250 mg group and 18.2% (4/22 patients) in the placebo group. The proportion of these patients was lower in the 375/125 mg group compared to that in the placebo group; however, the number of patients in the part was small and it was not possible to draw a conclusion.

The effect of preventing the worsening of COVID-19 symptoms was assessed in patients with SARS-CoV-2 infection with mild symptoms only. The proportion of patients whose 8 symptoms of COVID-19 or pyrexia (fever) according to temperature assessment were found to have worsened by day 10 of taking the drug tended to be lower in the 375/125 mg group (15.6%) and 750/250 mg group (15.5%) than in the placebo group (21.5%).

3.4.3 What were the side effects?

In this part, no patients experienced serious side effects or died during the study.

The number of patients who experienced side effects and stopped taking the drug was 1 (drug eruption) in the 375/125 mg group and 1 (headache) in the 750/250 mg group, but later, these side effects resolved or were resolving.

The incidences of side effects in patients with asymptomatic SARS-CoV-2 infection or with SARS-CoV-2 infection with mild symptoms only were 23.4% in the 375/125 mg group, 37.1% in the 750/250 mg group and 7.0% in the placebo group.

The side effects with incidences of 2% or more were decreased high density lipoprotein with an incidence of 17.4% in the 375/125 mg group, and decreased high density lipoprotein with an incidence of 32.7%, increased blood bilirubin and increased blood triglycerides with an incidence of 2.5% each and diarrhea with an incidence of 2.0% in the 750/250 mg group, and there were no side effects with incidences of 2% or more in the placebo group.

No major problems with the safety of Xocova tablets were found.

4. HOW HAS THIS STUDY HELPED OR WILL HELP PATIENTS AND RESEARCHERS?

The results are limited to the particular participants enrolled in this study and cannot be assumed to be true for everybody in general. Also, only the results of this study are included in this document. New information on or different results about the study drug may become or have become available from other studies. However, this research may help future SARS-CoV-2 infection patients and families by helping researchers understand more about each drug being studied.

In Japan, Xocova tablets received emergency authorization (dated 22 Nov 2022) based on the efficacy estimated from the interim results of the phase 3 part, and the efficacy was later verified by the final results of the phase 3 part. There were no particular safety concerns reported from the subsequent clinical studies or from the real-world experience since the emergency approval, and Xocova tablets received formal approval (dated 05 Mar 2024) as a drug for treatment of COVID-19 and has been in clnical use.

5. ARE THERE PLANS FOR FURTHER STUDIES?

Other studies using Xocova tablets are being done in patients with a risk of SARS-CoV-2 infection becoming severe and in child patients with SARS-CoV-2 infection. A study of the effect of Xocova tablets for preventing SARS-CoV-2 infection in members of the household of people with SARS-CoV-2 infection is also being done.

6. WHERE CAN I FIND MORE INFORMATION ABOUT THIS STUDY?

You may find more information about this study:

Website	URL	Identifier
The Japan Registry of Clinical Trials (jRCT)	Japanese: https://jrct.niph.go.jp/latest-detail/jRCT2031210350	jRCT2031210350

Contact information for the company that conducted this study:

The company’s name: Shionogi & Co., Ltd.

The company’s address:

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