INFORMED CONSENT FORM
AND
AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

Sponsor / Study Title:	**Shionogi* / "A Phase 3, multicenter, randomized, double-blind, 24-week study of the clinical and antiviral effect of S-217622 compared with placebo in non-hospitalized participants with COVID-19"** **Study Name: SCORPIO-HR** ** Shionogi may be one or more of the following companies.* *Shionogi & Co., Ltd. 1-8, Doshomachi 3-chome, Chuo-ku, Osaka 5410045, Japan* *Shionogi Inc. 300 Campus Drive, Florham Park, NJ 07932 USA* *Shionogi B.V. Herengracht 464, 1017 CA, Amsterdam, Netherlands*
Protocol Number:	**ACTIV-2d/A5407**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

KEY INFORMATION	The study doctor is being paid by the Sponsor to conduct this study.
PURPOSE	This is a research study and your participation in this study is voluntary. This form provides an overview of the study and its requirements. The purpose of this study is to evaluate the ability of an experimental oral drug called S-217622 to improve the health of people with coronavirus disease 2019 (COVID-19). We also want to see if this study drug is safe, and if this study drug can shorten the time you have COVID-19 symptoms, reduce the amount of virus in the body, prevent long COVID and prevent hospitalization or death.
STUDY DRUG	Study drug will be either an active study drug or a placebo. A placebo looks like a "real" drug, but it does not have any active study drug in it. This study will evaluate S-217622, an experimental drug that targets the virus that causes COVID-19 and may reduce the virus's ability to reproduce. This study drug is taken for 5 consecutive days by mouth. If you enroll in this study, you will receive S-217622 or a matching placebo.

NUMBER OF PARTICIPANTS	The study will enroll approximately 2000 participants. Approximately 1000 participants will be assigned to take S-217622 and approximately 1000 participants will be assigned to take placebo. This assignment will be random, and the study participant, the study doctor or study staff will not choose the assignment and will not know if you are receiving S-217622 or the placebo. However, in case of emergency, the study doctor can find out this information. Participants must be at least 18 years of age to participate in this study.
LENGTH OF STUDY	Your participation in this study will last up to 24 weeks.
REQUIRED ACTIVITIES	If you are in this study, the following study procedures are required: o You will record your symptoms o You will provide blood samples o You will have nasopharyngeal swabs (deep nasal swabs), and swabs of the front of the nose (anterior nasal swabs) collected by study staff
RISKS	The risks of S-217622 include nausea, diarrhea, headache, abdominal pain, a temporary increase in a type of fat in the blood called triglycerides and a temporary decrease in a type of cholesterol in the blood (high-density lipoprotein [HDL]), known as “good cholesterol”. Rarely, participants taking S-217622 have developed a rash. The study drug can interact with other medicines, and for this reason, you will need to tell the study doctor or study staff about any other medicines you are taking. Medicines that may have a concerning interaction with S-217622 will need to be stopped if this can be done safely.
BENEFITS	If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you will receive no benefit from being in this study and a 1 out of 2 chance that you receive an inactive ‘placebo’. There is a potential that S-217622 will not be effective in treating COVID-19 symptoms and will not reduce the risk of hospitalization and death. Information learned from this study may help others who have COVID-19.
OTHER CHOICES	Instead of being in this study, you may have the option of: • Treatment with drugs including COVID-19 therapies available to you locally through your healthcare provider by prescription: (**Outside of US**) Treatment with available COVID-19 drugs. The study staff will let you know about approved options that may be available to you locally, outside of the study by prescription from your healthcare provider.

(US only) You will be eligible for this study if you are considered at standard risk for severe COVID-19 and have none of the risk factors that would put you at higher risk of disease progression.

- Treatment with other experimental drugs if you qualify and if these studies are available to you.
- No treatment
- If you choose to take certain approved or authorized medications to treat COVID-19 that are available to you **before enrolling** in the study, you will not be able participate in this study
- You can also choose to take other locally available standard of care COVID-19 therapies **after enrolling** in the study including outpatient IV remdesivir, molnupiravir, monoclonal antibodies (if in use) or other oral treatments as long as they are compatible with the study drug, if these are available to you. The study team can let you know what medicines are not safe to take with the study treatment.
- You will **not** be able to take part in the study if you are going to take nirmatrelvir plus ritonavir **(US only)** which is authorized and recommended for early-stage treatment of mild to moderate COVID-19 among persons at high risk for progression to severe disease), hydroxychloroquine, or ivermectin, because these medications may interact with S-217622 and may cause side effects or illness. Please discuss any COVID-19 medications you have taken or plan to take with your study doctor.
- Individuals who are unvaccinated against COVID-19 are particularly at high risk for progression to severe disease and should know that they will not be able to receive treatment with Paxlovid if they participate in this study.

Please read this Informed Consent Form (ICF) carefully

INTRODUCTION

You are invited to take part in a research study of an experimental drug called ensitrelvir (S-217622) that is being developed for the potential treatment of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The sponsor of this study is Shionogi (Sponsor). The National Institute of Allergy and Infectious Diseases (NIAID), an institute of the National Institutes of Health (NIH), as represented by the Division of AIDS (DAIDS) (hereinafter referred to as “NIH”) is also a funder of the study.

The plan for this study was reviewed and approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), which is a group of scientific and non-scientific people who protect the rights and wellbeing of people who take part in research studies.

Before you decide whether to take part in the study, we would like you to understand why this research study is being performed and what it would involve for you. One of our study staff will go through this ICF with you and answer any questions you have. If you would like more information, or if there is anything you do not understand, please speak to the study doctor, or study staff. You may take an unsigned copy of this ICF home with you to read in your own time. Take your time to think and talk about the study with your family, friends, and your regular doctor before making your decision. If you decide to take part, a study staff member will ask you to sign and date the ICF at the end of this document. By signing and dating this ICF, you agree to take part in this study and authorize use of your protected health information (PHI) specifically for carrying out the activities of this research. You will receive a copy of this signed and dated form.

1. What is the purpose of the study?

COVID-19 is a disease caused by infection with a coronavirus called SARS-CoV-2. COVID-19 affects people in different ways. Infected people have had a wide range of symptoms reported – from no symptoms or mild symptoms to severe illness needing hospitalization, and sometimes death. Severe illness is due to inflammation in the lungs (pneumonia) and damage to organs due to inflammation and blood clots.

Fever or chills, cough, shortness of breath or difficulty breathing, runny or stuffy nose, sore throat, muscle pain, diarrhea, nausea, headache, muscle or body aches, and new loss of taste or smell are typical symptoms for this condition. These symptoms usually occur a few days after infection with SARS-CoV-2 and the virus can easily be spread to others before symptoms are noticed. SARS-CoV-2 can also cause symptoms for more than three months, this is called "long COVID".

This study is being performed to evaluate the safety, efficacy, and pharmacokinetics (PK) (the way that the body handles the study drug) of a new experimental drug called S-217622; we will refer to the PK part of the study as the PK "sub-study". This study drug, a 3CL protease inhibitor, has been shown in animals to slow the growth of the virus and prevent the infection from becoming severe. It is designed as an antiviral specific to SARS-CoV-2. Proteases are enzymes that breakdown proteins. Some viruses rely on proteases to make copies of themselves. S-217622 blocks a protease called 3CL protease that the SARS-CoV-2 virus (the virus that causes COVID-19) uses to make copies of itself. We want to learn if giving S-217622 by mouth within 3 days of symptom onset can shorten the time you have COVID-19 symptoms, reduce the amount of virus in the body, and prevent hospitalization or death.

This study will include both people at standard and higher risk of severe COVID-19 infection. People are at higher risk of developing severe illness if they are 65 years of age or older, have pre-existing conditions such a high blood pressure, heart disease, being overweight, diabetes, kidney problems, lung diseases such as asthma and chronic obstructive pulmonary disease (COPD), cancer, are immunocompromised (when the immune system's defenses are low,

affecting one's ability to fight off infections and diseases), or take steroids regularly. People are considered at standard risk of severe disease if they do not have any of these risk factors.

S-217622 is an investigational drug. "Investigational" means that the study drug is still being tested but has obtained emergency regulatory approval from the Pharmaceuticals and Medical Devices Agency [Japan PMDA]. A study completed in Japan showed that S-217622 led to faster symptom resolution and clearance of the virus compared to placebo. However, since this study was conducted in Asian countries and did not include many participants with illnesses that would make them high risk for severe COVID-19, it is necessary to do further studies in a wider patient population globally and include participants with risk factors for severe COVID-19. More information is also needed on long COVID, and this study will explore long COVID with a week 12 and week 24 follow up.

S-217622 has not been approved for use by the United States Food and Drug Administration [US FDA], the European Medicines Agency [EMA], or any other country authorities outside of Japan. S-217622 is given in oral form as tablets.

S-217622 will be compared to placebo tablets. The placebo is a substance that looks just like S-217622 and is given in the same way but it has no active ingredient in it. The placebo will not harm you but is necessary to compare with S-217622. In this consent form, we will refer to the experimental drug, S-217622, and placebo as "study drugs". You will be assigned by chance (like flipping a coin or rolling dice) to receive S-217622 or placebo and will have a 1 out of 2 chance of receiving S-217622 and a 1 out of 2 chance of receiving placebo. You and the study team will not know whether you are getting the experimental drug (S-217622) or placebo. The study doctor can find out this information in case of an emergency. S-217622 and the matching placebo will be provided as white, round 125 mg tablets; you will take 3 tablets (375 mg) on Day 1, followed by 1 tablet daily (125 mg) on Days 2 through 5.

You have been asked to take part in this study because in the past 3 days, you have been diagnosed with COVID-19 and have symptoms due to COVID-19, and you have not yet received treatment for your infection, other than for symptomatic relief.

<u>Pharmacokinetics (PK) – measuring the quantity of S-217622 in a blood sample) Sub-study:</u>
A total of 400 participants will take part in the PK sub-study, and each will be assigned to 1 of 2 groups. Depending on when you enroll into the main study, you may be assigned to 1 of the groups, or you may not take part in the sub-study at all if 400 participants have already taken part at that point. The study staff will inform you if you will be participating in the PK sub-study.

The 2 groups differ in the amount of blood that is collected for the sub-study and in the total number of participants. The first group will have 150 participants who will have blood drawn at set times on Day 1 (2 times), Day 4 (2 times), and Day 8 (once). The second group will have 250 participants who will have blood drawn on Day 1 (once), Day 4 (once), and Day 8 (once). Your PK samples may be kept for up to 2 years.

2. Do I have to take part? What will happen if I don't want to carry on with the study?
Your taking part in this study is voluntary. You can choose not to take part in this study. Even if you agree to take part in the study, you are free to leave the study at any time, without giving a reason. Leaving the study will not affect your care or any benefit you should receive, now or in the future.

If you decide to withdraw consent and stop the study early, please tell the study doctor or study staff immediately. You will be asked to return to the study site to have final tests completed. You will be asked to return the blister pack with any unused study drug to your study doctor or study staff. Tell the study doctor or study staff if you have any side effects for up to 28 days after you stop taking the study drug. The study doctor or study staff will add that information to your study record.

If you withdraw from the study, the Sponsor can use the data collected up to your withdrawal. You can withdraw your permission for the data to be used by requesting this in writing to your study doctor. However, it will not be possible to delete your data from the results of the completed analyses. Your authorization for release of your PHI expires at the end of this study.

Your authorization for release of your PHI during the study, as it relates to this research study, does not expire unless you cancel it in writing to your study doctor listed on the first page of this form.

3. Where will the study take place and how long will it last?
The study will last up to 24 weeks.

Your study visits will take place in person or remotely. You and the study staff at your study site will discuss the location for each visit.
- In-person visits will take place at the clinic, at your home, or at another non-clinic location.
- Remote visits may take place over the phone or through telemedicine systems approved for use at your site.

Approximately 2000 participants will take part in the study at approximately 200 study sites in North America, South America, Europe, Africa, and Asia.

During the study, a group of experts from outside of the study will regularly review the safety of the study drugs and if they are effective or not. If they determine the study drug is not safe or effective, you will be informed, and the study doctor will stop giving the study drugs.

4. What will I be asked to do if I decide to take part?
It is important that you tell the study doctor or study staff if you have been in another study in the past or are currently in another study. There are reasons such as potential medication interactions that will help your study doctor determine if you are eligible to take part in this study.

If you are being treated by a medical provider, we would like your permission to contact that medical provider to let them know that you are taking part in this study. It is important for your regular medical provider to know that you are in a study and what study drugs you will be taking.

If you have symptoms after the study ends or if you stop the study early, your regular medical provider may want to contact the study staff.

If you agree to take part in the study, it is important, for your safety, that you must:

- Follow the instructions you are given.
- Give correct and accurate information about your medical history and current medical condition.
- Tell the study doctor or study staff about any changes in the way you feel, your health, or your diet during this study.
- Not take certain medications as discussed with you by your study doctor or study staff. This includes certain prescription and over-the-counter drugs (including vitamins and herbs).
- Tell the study doctor or study staff about any new medicine or medication (including prescription, over the counter, and “natural” treatments) you take during the study. Do not start any new medications during the study until you have discussed it with your study doctor. Tell the study doctor or study staff about any changes in your medications (including a change in how much of a medication you are taking and stopping or starting a prescribed medication, over the counter or “natural” treatments) during the study.
- Take the study drug as instructed.
- Do not give your study drug to anyone else.
- Keep study drug out of the reach of children.
- Come to all study appointments.
- Complete your diary on time as instructed by the study staff.
- Return unused study drug and all empty packages to your study doctor or study staff at each study appointment.
- Allow the study doctor or study staff to contact you and ask how you are doing and to follow-up regarding your diary entries.
- Agree to use acceptable methods of birth control if needed. The study doctor or study staff will explain acceptable birth control methods to you (also refer to "Pregnancy risks" in the section below).
- Not participate in another interventional study (study that provides medications or other treatments) for 28 days after enrollment or up to the time of hospitalization.
- Allow your study information to be linked with the study information from people who live in the same household as you and who have also agreed to enroll in this study.

Additionally,

- **If you are hospitalized**, you may receive any non-study COVID-19 treatments prescribed by your treating physician(s) and available to you
- **If you are not hospitalized**, you must not receive COVID-19 medicines (some of which are approved or authorized, and some of which are not) which may have drug interactions with the study treatment; these include Paxlovid, hydroxychloroquine, and ivermectin. Other locally available COVID-19 treatments can be taken as long as there are no known drug interactions with the study treatment and include:
    - COVID-19 monoclonal antibodies (if currently available), outpatient administered IV remdesivir, molnupiravir, convalescent plasma, fluvoxamine, favipiravir, and inhaled

budesonide. The study staff will tell you if there is a possible drug interaction with locally provided COVID-19 treatment**.**

- **You cannot take part in the study if you are already taking a COVID-19 treatment before joining the study.** Medicines that are used for COVID-19 symptoms, like cough medicine and pain relievers are allowed before joining the study.

5. What will happen to me if I take part?

This ICF tells you what you will need to do in each of study periods. However, please understand that extra visits may be scheduled at any time during the study if your study doctor decides that it is necessary for additional tests, blood draws, or examinations to be performed for safety reasons. The amount of blood drawn will depend on what blood tests will be needed at that extra visit.

Information Collected at Screening

There is some information that we collect on everyone who is screened for this study. As part of your screening visit, some demographic (for example, age, gender, race, ethnicity), clinical (for example, disease condition, diagnosis), and laboratory values will be collected from you.

We will collect this information even if you do not enroll in this study. This information is collected so that researchers may determine whether there are patterns and/or common reasons why people do not join a study.

Blood Drawn

The study staff can tell you how much blood will be collected at any particular visit. Total blood volume collected during this study is about 166 mL or about 34 teaspoons; If you are assigned to one of the PK sub-study groups, a total of 10 mL or about 2 teaspoons more will be collected for the first group and a total of 6 mL or about 1 teaspoon more will be collected for the second group.

Note About Location of Study Visits:

The study staff will talk to you about where your study visits will take place. In-person visits are planned for Screening, Days 1, 4, 8, 16, 29, Week 12, and Early Discontinuation. An additional in-person visit (if applicable) will be scheduled if your symptoms worsen at any time between Day 6 and Day 29. An extra visit (if applicable), if you are re-infected after Day 29, will take place at the clinic, at your home, or another non-clinic location if available.

Screening Visit

If you would like to be in this study, after you have read, signed, and dated this consent form, you will have a screening visit to make sure you meet the requirements for joining the study. This visit will take about 1 hour.

At this visit:

- Study staff will review your medical history and confirm that you have tested positive for SARS-CoV-2 infection.
- You will be asked about symptoms you are experiencing.

- You will be asked about any COVID-19 treatment you have already received or intend to receive.
- You will be asked demographic questions, including your race and ethnicity.
- You will be asked about any health conditions you have, and about your health in general.
- You will be asked you about your medication history and any medications you are taking.
- You will be asked about your smoking status.
- You will have your height, weight, and oxygen level measured.
- You will be asked if you have received or if you plan to receive monoclonal antibodies or outpatient IV remdesivir treatment for COVID-19.

Entry Visit

If you qualify for the study, you will have a study entry visit. This visit might occur on the same day as your screening visit, but no more than 72 hours (3 days) after Screening. At this visit, you will be randomly assigned (like flipping a coin or rolling dice) to a study group. You will have a 1 out of 2 chance of receiving S-217622 and a 1 out of 2 chance of receiving placebo. You and the study staff will not be able to choose whether you get S-217622 or placebo. You and the study staff you interact with, including the study doctor, will not know whether you are receiving S-217622 or placebo.

Also, at the Entry visit:

- You will be asked if you have received or if you plan to receive monoclonal antibodies or outpatient IV remdesivir treatment for COVID-19.
- You will have your weight and oxygen level measured.
- You will have a physical examination and answer questions about your medical history and any medications that you are taking or have taken in the past
- You will be asked about any COVID-19 treatment you have already received or intend to receive.
- You will be asked about symptoms you are experiencing now, as well as symptoms you had prior to having COVID-19 infection.
- The study staff will ask if anyone else in your household has been diagnosed with SARS -CoV-2 infection.
- You will be asked to provide your home address.
- You will be asked to provide contact information for at least 2 people the study staff can contact in case we cannot reach you for a study visit. You will need to tell these people that you are in the study, and that they could receive a call from study staff. If study staff cannot reach you after 2 tries (separated by 24 hours), they will call 1 of the people you have identified.
- You will be asked to provide your healthcare provider contact information, like your regular medical provider or commonly used clinic and hospital and give permission to contact these providers about the medicines that you take and any care or hospitalization you may receive for your COVID-19 infection.
- You will receive a kit that includes information about the study, instructions on what to do if you have worsening symptoms, and contact information for the study staff.
- You will complete your first study diary entry with the study staff to make sure that you understand how to use the diary.

- 4 swabs will be collected from your nose. All 4 swabs are used to detect viruses. 3 swabs will be deep swabs, and the other swab will be a shallow swab of your nostril. For the deep swabs, the study staff will insert a swab into your nostril. The swab will be placed deep towards to the back of your throat. The swab will be left in place for several seconds and then slowly removed. This procedure may be uncomfortable, and it might make you gag or make your nose bleed. For the shallow nostril swab, the swab will be inserted and rotated along the inside of your nostril.
- You will have blood drawn. This blood will be used for study-required testing such as for Hepatitis B and C. The study doctor may be required by law to report any positive results of these tests to local health authorities. Your blood will also be drawn for routine safety tests. Your blood will also be used to conduct a SARS-CoV-2 antibody test.
- If you are a woman who can become pregnant, a urine or blood pregnancy test will be done.
- If you are included in the first group of the PK sub-study, you will have blood drawn after 60 minutes of taking the study drug and then a second blood draw after 90 minutes of taking the study drug.
- If you are included in the second group of the PK sub-study, you who will have blood drawn after 60 minutes of taking the study drug only.
- You will be given 5 days of study drug to take during the study and will be asked to take the first dose during your study visit.
- You will start study drug no more than 3 days after your COVID-19-related symptoms began. You will start maintaining the study drug diary from the first time you take study drug. Details of this are provided in the next part of the consent.
- You will be asked about any study drug side effects or symptoms that you may be experiencing.

<u>Daily on Days 1 to 29</u>
You will record your symptoms in your study diary at about the same time every day. You will also record if you visited an emergency room or clinic or if you were hospitalized. If you are not feeling well, someone can help you by completing the responses for you, but the responses should come from you. You will use an electronic device (such as a smartphone) to complete the diary, using an app. If you do not have access to a smartphone, the site will provide one for your use to complete the electronic diary. Standard message and data fees may apply. If the electronic diary is not available, then you will be expected to complete a paper diary.

You will receive a reminder every day on Days 1 to 29 to complete your study diary. This reminder may be by telephone, text message, email, or other methods that you give permission for.

<u>Study Visits on Days 4, 8, 16, and 29</u>
At these visits:
- You will have your weight measured (Days 4, 8, and 29)
- You will have a brief physical exam and answer questions about any medications you are taking.
- You will be asked about any COVID-19 treatment you have already received.

- You will be asked about any study drug side effects or symptoms that you may be experiencing.
- You will be asked if there are any updates to the contact information for the people you have identified.
- You will review the entries in your study diary with study staff. The study staff will collect your diary on Day 29.
- You will complete questionnaires about your quality of life and physical and emotional health to understand how COVID-19 might have impacted these. (Day 29)
- You will be asked if anyone else in your household has been diagnosed with SARS-CoV-2 infection (Days 8 and 29).
- You will have blood drawn. This blood will be used for study-required testing, routine safety testing.
- You will have blood drawn if you are a woman who can become pregnant, to confirm you are not pregnant (Day 29).
- If you are included in the **first group** of the PK sub-study, you will have additional blood drawn prior to taking the study drug, and between 60 and 90 minutes of taking the study drug on Day 4. You will also have additional blood drawn anytime on Day 8.
- If you are included in the **second group** of the PK sub-study, you who will have additional blood drawn after 60 minutes of taking the study drug at Day 4, and a single blood draw on Day 8.
- You will have 3 deep nasal swabs collected by study staff to evaluate the amount of SARS-CoV-2 virus recovered from your nose. (Days 4, 8, and 16)
- The study staff will review your study drug log (Days 4 and 8).
- You will be asked to return your unused/empty drug packages (Day 8).

<u>Study Visit at any time between Day 6 and Day 29 if you have worsening symptoms after stopping study treatment</u>

If you are asked to return, you will complete the following:

- You will be asked about any study drug side effects or symptoms that you may be experiencing.
- You will have 3 deep nasal swabs collected by study staff to evaluate the amount of SARS-CoV-2 virus recovered from your nose.
- You will be asked questions about any medications you are taking.
- You will be asked about your COVID-19 symptom severity
- You will have blood drawn. This blood will be used for study-required testing and routine safety testing
- You will review the entries in your study diary with study staff.

<u>Study Visits at Weeks 12 and 24</u>

These visits are very important as they allow an assessment of the occurrence of long COVID. At these visits:

- You will be asked about any study drug side effects or symptoms that you may be experiencing.
- You will be asked if there are any updates to the contact information for the people you have identified.

- You will answer questions about any potential COVID-19 related symptoms or conditions you have experienced, including questions about your quality of life and physical and emotional health.
- You will have your weight measured. You will have blood drawn for study-required testing, and if you are a woman who can become pregnant, to confirm you are not pregnant (Week 12).
- You will return the electronic diary if one was provided by your study doctor.

<u>If you are reinfected with SARS-CoV-2 after you have completed study treatment</u>
If you are asked to return, you will complete the following:
- You will have a brief physical exam and answer questions about any medications you are taking.
- You will be asked about any study drug side effects or symptoms that you may be experiencing
- You will have blood drawn. This blood will be used for a SARS-CoV-2 antibody test
- You will have 1 deep nasal swab collected by study staff to evaluate the amount of SARS-CoV-2 virus recovered from your nose (Only collected if the diagnosis of reinfection is within 7 days of symptom onset suggesting reinfection).

<u>Leaving the Study Early</u>
If at any point you want to stop participating in the study, you should contact the study site immediately. The study staff may ask you to return for some study visits and procedures.

<u>If you leave the study before Day 29:</u>
- You will have your weight measured
- You will have a brief physical exam and answer questions about any medications you are taking.
- You will be asked about any study drug side effects or symptoms that you may be experiencing.
- You will review the entries in your study diary with study staff. The study staff will collect your diary.
- You will be asked if anyone else in your household has been diagnosed with SARS-CoV-2 infection.
- You will have 1 deep nasal swab collected by study staff to evaluate the amount of SARS-CoV-2 virus recovered from your nose.
- You will have blood drawn. This blood will be used for study-required testing, routine safety testing, a SARS-CoV-2 antibody test, and if you are a woman who can become pregnant, to confirm you are not pregnant.
- You will be asked the reason why you are leaving the study early

<u>If you leave the study after Day 29:</u>
- You will have a brief physical exam and answer questions about any medications you are taking.

- You will be asked about any study drug side effects or symptoms that you may be experiencing.
- You will answer questions about any potential COVID-19 related symptoms or conditions you have experienced, including questions about your quality of life and physical and emotional health.
- You will have blood drawn for study-required testing, and if you are a woman who can become pregnant, to confirm you are not pregnant.

If you have not withdrawn consent but the study staff cannot reach you, the study site will try to obtain information regarding whether you are living or have died from other sources, such as family members and other secondary contacts that you have provided, or medical records.

WHAT IF THE STUDY SITE CAN NO LONGER REACH ME DURING THE STUDY?
If you cannot be reached after 2 attempts to contact you (with 24 hours between attempts), study staff may try to contact you through the family, friends, or acquaintances you provided at screening and updated at each visit.

If you are still unable to be reached, we will attempt to obtain information about your status (whether you are living or have died) by contacting your healthcare provider (if you agree) or by accessing publicly available records (you do not have to give your permission for us to access these records).

6. What will happen to the samples I give?
The Sponsor will use any blood, nasopharyngeal or nasal swabs, and urine samples collected from you for the purposes of this research study. To protect your privacy, your samples will be labelled with your participant identification (ID) and study number only.

Some of the samples that are collected from you will be analyzed using tests that are not yet approved by the US FDA, or any other regulatory agency and are considered “research” tests. Therefore, the testing may be conducted once the tests have been approved. For these reasons, you will not receive the results of the tests to:

- Check levels of SARS-CoV-2 or other viruses in your nasal swabs.
- Check if your body developed antibodies to SARS-CoV-2.
- Detect small genetic differences in the SARS-CoV-2 virus in your nasal swabs, which may help the Sponsor understand how different subjects will respond to treatment with S-217622. No genetic information from you will be collected.

Your samples will not be used outside the evaluation of S-217622.

Your samples (blood and nasal swabs) collected during this study may be used for research that leads to profit for the Sponsor. You will not share in this profit. These specimens will not be sold for commercial profit

Blood and nasal swab specimens will be shipped to central laboratories designated by the Sponsor for analysis and for storage. Research results, including individual research results, will not be disclosed to you.

If you decide you do not want your blood samples analyzed or if you withdraw consent, you can request that your samples be destroyed at any time. However, if you request to have your samples destroyed during the study, there is a possibility you will be asked to discontinue the study, so please be aware.

7. What are the possible disadvantages and risks of taking part?

There are risks to taking part in this research study. If you receive placebo (the inactive substance) as part of this study, your symptoms of COVID-19, may not improve or may get worse. One risk is that the study drug S-217622 may not stop you from becoming sicker, being hospitalized, or dying from COVID-19. These study drugs may not be as effective as currently approved or authorized medications in preventing you from becoming sicker and/or needing hospitalization.

Risks Associated with S-217622:

S-217622 is a class of drug called a 'protease inhibitor'. Protease inhibitors have been used in other infections such as HIV and Hepatitis C, as well as SARS-CoV-2 treatment. In the case of HIV treatment, protease inhibitors have been given over more than 2 decades and have been associated with high cholesterol and heart disease. However, since S-217622 is only given over 5 days, these side effects associated with other protease inhibitors are likely not relevant.

As of 01 March 2023, no deaths were reported by people taking S-217622 or placebo. Other serious unwanted effects, which occurred in 1 participant taking S-217622 (heavy menstrual bleeding) and 1 participant taking placebo (cholecystitis acute), were considered unrelated to S-217622 or placebo. Most effects after taking S-217622 or placebo have been mild or moderate and have either all gone away or are getting better.

Shionogi has conducted a clinical study in 201 healthy adult male and female participants and healthy elderly male and female participants to investigate the safety, tolerability, and pharmacokinetics (PK) of S-217622. PK tests look at how the study drug moves through (or is absorbed by) your body and how the body processes (or what is the effect of) the study drug in your body. Shionogi has conducted a drug-to-drug interaction study in 14 healthy adult participants to see if any drugs interact with S-217622.

A study in 2942 participants with COVID-19 infection with no symptoms (asymptomatic) or mild to moderate COVID-19 to investigate efficacy, safety, and PK is completed and the results allowed the emergency approval of S-217622 in Japan for SARS-CoV-2 infection, follow up in the study to assess long COVID is still ongoing. All side effects were mild or moderate and participants recovered without any treatment.

The most frequent side effects of S-217622 were:

- A temporary decrease in high density lipoprotein (HDL, "good" cholesterol) in 1 of 4 participants
- A temporary increase in blood triglycerides (a type of fat found in your blood) in 7 of 100 participants

- An increase in blood bilirubin in 7 of 100 participants. Bilirubin is produced by the liver and S-217622 causes a harmless increase of bilirubin in the blood which returns to normal after stopping study treatment. There are no symptoms caused by these increased levels.

Other side effects of S-217622 reported in less than 3 out of 100 participants with COVID-19 include:

- Headache
- Diarrhea (loose, watery stools)
- Abdominal Discomfort
- Dyspepsia
- Nausea
- Vomiting
- Drug eruption
- Eczema
- Pruritus
- Urticaria
- Blood iron increased
- Dyslipidemia
- Blood creatine phosphokinase increased

As S-217622 has been given emergency approval in Japan, as of 01 March 2023 over 20,000 people with COVID-19 have been treated. No treatment related deaths or treatment related serious adverse events have been reported.

Pregnancy risks:

S-217622 must not be given to a person who is pregnant. The effects of S-217622 on an unborn or nursing child are currently not known. The study drug may involve risks to the embryo or fetus if you become pregnant.

In studies where pregnant animals were given higher doses of S-217622 than those in this study, findings included: higher rates of skeletal problems, delayed development of the offspring, and higher rates of offspring deaths. For this reason, highly effective contraception must be used, and a pregnancy test will be performed to make sure that female participants are not already pregnant.

Therefore, it is important that you take measures to make sure you do not become pregnant while participating in the study. If you can become pregnant and you are not planning to take precautions against pregnancy, or if you are pregnant or are breastfeeding, you will not be allowed to take part in this study.

Hormonal contraception including oral contraception, transdermal, intravaginal, and injectable contraception must not be used alone and should have an additional barrier method like condoms used during the 2 weeks after taking the last dose of the study drug.

Hormonal contraception can be continued during study treatment. The interaction of the study treatment with different types of hormonal contraception is still under evaluation and study treatment may lead to an increase or decrease of hormonal contraception levels

If you can become pregnant and are engaging in sexual activity that could lead to pregnancy, you must agree to use effective contraception and not to donate your eggs for reproduction from study entry through 2 weeks after the last dose of study drug. In addition, if you can become pregnant and are engaging in sexual activity that could lead to pregnancy you will undergo a urine or blood pregnancy test that will be performed prior to administration of study drug at study entry, at Day 29, at Week 12, early termination or premature study discharge, and any time pregnancy is suspected during the study.

If you become pregnant during the study, there may be risks to both you and/or your unborn child, and these risks are not known. If you are female and no longer taking S-217622 and wish to become pregnant during the study, please consult your study doctor or study staff.

If you are found to be pregnant while taking the study treatment or up to 2 weeks after the last dose of study treatment, the study treatment will be stopped immediately (if it has not already been completed). Your pregnancy will be followed by the study team to the outcome of the pregnancy.

You should discuss any pregnancy plans with your study doctor before you agree to be in this study.

Additionally, you must agree to the following as instructed by your study doctor or study staff for the time you are receiving S-217622:

- If you are female sex at birth and if you are participating in sexual contact that may lead to pregnancy, you must agree to use an effective form of birth control that is not hormonal contraception, which may be affected by a possible drug interaction with the study treatment. Effective contraception methods include:
    - Intrauterine devices (IUDs)
    - Barrier methods such as condoms with or without spermicide or cervical cap
    - Diaphragm, or sponge with spermicide

You must use 1 effective form of birth control as described above from study entry up to 2 weeks after the last dose of the study drug.

The only participants who will be exempt from the birth control requirement are those women who are unable to become pregnant, or those who are not participating in sexual contact that may lead to pregnancy:

- Persons who have had a hysterectomy (uterus removed), bilateral oophorectomy (both ovaries removed), bilateral salpingectomy (both fallopian tubes removed), or bilateral tubal ligation (tubes tied) and documentation of the procedure.
- Postmenopausal persons in the appropriate age group who had their last period more than 1 year before start of the study treatment.
- If your partner has had a vasectomy and has had a follow-up check showing zero sperm count, then you do not need other birth control.

If you are abstinent or not participating in sexual contact that may lead to pregnancy, you must agree to use an acceptable method of birth control if you start having sex that may lead to pregnancy during the study.

Unknown risks:
If you take S-217622, it is possible that you could have problems and side effects of S-217622 that nobody knows about yet.

It is possible that taking S-217622 with your regular medications or supplements may change how S-217622, your regular medications, or your regular supplements work.

Just like when you take any drug, there is a small risk that you could have an allergic reaction to the study drug. The study staff will ask you if you have had any previous reactions to drugs to help evaluate this risk.

Risks of combining the study drug with other medications

The study drug S-217622 can cause increases or decreases in the levels of other medications that could produce dangerous side effects or make the other medications not work as well. Thus, there is a risk of serious and/or life-threatening side effects when your regular non-study medications are taken with the study drugs. Due to this concern for drug interactions, there may be a medicine you take which can't be stopped and therefore you will not be able to take part in this study. Some medicines will need to be stopped for the first 6 days of the study and some for the first 28 days.

The study staff will review all of your current medicines and advise which medicines will need to be stopped. The study doctor and your regular provider can help decide if it is safe for you to stop these medicines in order to participate. Taking certain medications within the past 14 days before joining the study (or in some cases longer than 14 days) will prevent you from being in the study, due to the risk for drug interactions. The study staff will ask you about medicines you have taken and will let you know if any of the medications you have taken will prevent you from participating. If you are hospitalized to treat your COVID-19 infection, you may then be able to take these medications if your regular medical provider recommends treatment.

You can't use S-217622 outside of the study during the study participation (even if S-217622 is commercially available in the local region).

Examples of medications that cannot be taken from the time of informed consent to the completion of examinations on Day 29 (unless hospitalized) are listed below:

- Corticosteroids (such as dexamethasone) given by any route, including as a pill, an intravenous (IV, into a vein) infusion, as a nasal spray, as an inhaled medicine, or injected into a joint. Prednisolone and intranasal or inhaled beclomethasone (a steroid) will be allowed.
- Medications that are broken down by a specific enzyme called CYP3A: Examples include the following medications: alfentanil, avanafil, buspirone, chloroquine, conivaptan, darifenacin, darunavir, ebastine, everolimus, hydroxychloroquine, ibrutinib, ivermectin,

lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, and tolvaptan

Examples of medications that cannot be taken with the study drug due to the risks of an interaction that can make you ill or stop the drugs from working, (until 24 hours after stopping the study drug) include:

- Paxlovid
- Phenytoin and rifampin
- Digoxin, fexofenadine, loperamide, quinidine, talinolol, vinblastine, dabigatran, and doxorubicin
- 2 amino 1 methyl 6 phenylimidazo[4,5 b] pyridine, coumestrol, daidzein, dantrolene, estrone-3-sulfate, genistein, prazosin, sulfasalazine, daunorubicin, methotrexate, imatinib, and ketamine
- OAT 3 substrates with a narrow therapeutic window such as methotrexate

For your safety, you must tell the study doctor or study staff about all medications (whether prescription, over the counter, or herbal medications and supplements) you are taking before you start the study. You must also ask for approval before taking any new medication while you are on the study. Please ask the study doctor if you have any questions about the risk of combining the study drugs with other medications.

Risks of stopping your regular medication:
If you must stop your regular medication to participate in the study, the condition that the medication is used for might come back or get worse. Please tell the study doctor or study staff right away if you have any problems when you stop your regular medication.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drug. For your safety, you must tell the study doctor or study staff about all medications you are taking before you start the study.

Blood collection:
During this study, samples of your blood will be taken (most often by inserting a needle into a vein). There may be side effects of having blood drawn such as:

- Fainting
- Dizziness
- Redness
- Pain
- Swelling
- Bruising
- Bleeding
- Infection
- Nerve injury

If you feel dizzy or faint, tell the study doctor or study staff right away.

Nasopharyngeal or nasal swabs:
Such swabs are used to collect a sample from either nose (nasal) or area between your nose and upper throat (nasopharyngeal). They are used to test for coronavirus and other infections like influenza and respiratory syncytial virus (RSV). It is important that you tell your study doctor or study staff if you have nose or sinus problems, recent nose injury or surgery before the start of the study.

Nose discomfort and nosebleed are risks associated with this procedure. Your eyes may tear up during the procedure.

If you experience side effects during the study, please let the study doctor or study staff know:
To help keep you safe during the study, it is very important that you should get medical help and contact the study doctor or study staff if you have any of these side effects associated with study treatment or any other side effects during the study. If you do not understand what any of these side effects mean, please ask the study doctor or study staff to explain these terms to you.

Risks of transmitting personal information over the internet
As part of this study, you will be required to use an electronic diary. The electronic diary used in this study will transmit your personal information via the internet. You may also be asked to communicate with researchers via text message, email, or using a website. The diary and all other digital or web-based technologies used in this study are designed to secure your personal information from accidental loss and from unauthorized access, use, alternation, and disclosure.

Unfortunately, however, the transmission of information via the internet and mobile platforms is not completely secure and the security of your personal information transmitted using the study diary or website cannot be guaranteed.

While the Terms of Use for the electronic diary may include statements limiting your rights if you are harmed as a result of your use of the electronic diary in this study, you do not release the study doctor, Sponsor, institution, or agents from responsibilities for mistakes and do not waive any of your rights as a research participant.

8. What are the possible advantages or benefits of taking part in the study?
You may not benefit from the study, as participating in this study may or may not reduce symptoms of COVID-19 infection.

Even though you may not receive any benefit, other people may benefit in the future because of what the researchers learn from this study.

9. What are the alternative options for treatment?
Instead of being in this study you have the choice of:

- Treatment with drugs available to you from your healthcare provider including Paxlovid, which is recommended and authorized for outpatients with COVID-19 at high risk for severe COVID-19
- Treatment with other experimental drugs if you qualify

- No treatment
- There may be COVID-19 treatments available to you through an emergency use basis or a fully approved treatment. (US ONLY) Under an EUA, the US FDA may allow unapproved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions. Your study site will tell you about any COVID-19 treatments that might be available to you through an EUA or full approval, including locally available medicines for COVID-19 treatment.
- Oral medications, monoclonal antibody therapies and outpatient remdesivir (administered as an intravenous medication) are available in some places in the world for the treatment of mild to moderate COVID-19 in certain patients who are at higher risk for getting severely ill from COVID-19, including hospitalization or death. The US NIH COVID-19 Treatment Guidelines Panel recommends use of the available EUA oral therapy nirmatrelvir/ritonavir (Paxlovid) and outpatient IV remdesivir for the treatment of non-hospitalized patients with mild to moderate COVID-19 who are at high risk for getting severely ill from COVID-19, as they have been shown to reduce hospitalizations and deaths from COVID-19 by as much as 85%-87% in some studies. (https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/nonhospitalized-adults--therapeutic-management/) The oral therapy molnupiravir is also recommended and has shown 30% efficacy to reduce hospitalization and death In a study conducted before the current circulating Omicron variants. The US NIH COVID guidelines no longer recommend the monoclonal antibody bebtelovimab. The US Centers for Disease Control and Prevention (CDC) has a list of the conditions that make it more likely to get severely ill from COVID-19 (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html). Such conditions may allow you to access oral treatments, monoclonal antibody therapies, or remdesivir under EUA if you have risk factors for severe COVID-19. If you prefer to seek treatment outside of the study, the study staff will provide information to you on local clinics or other places that are providing oral medications, monoclonal antibodies, or other authorized treatments if available. If you receive COVID-19 treatment before enrolling in the study, you will not be able to join the study.

Please talk to your study doctor about these and other choices available to you. Your study doctor will explain the risks and benefits of these choices.

10. Why would I need to stop being in the study?

The Sponsor, your study doctor, the NIH, the Office for Human Research Protection (OHRP), or regulatory authorities (like, the Japan PMDA, the US FDA, the EMA, and other country authorities) have the right to take you out of the study at any time (early termination) with or without your agreement. These decisions will be made if:

- You do not follow instructions
- The study is terminated
- It is in your best medical interest to stop your participation
- You do not consent to any testing or examination required in this study
- You cannot attend planned clinic visits
- If you revoke your consent to disclose your PHI (refer to "How will my personal information be protected?" in the below section)
- If we should find out that you should not be in the study for any reason

If you develop side effects to the study treatment or if you need a treatment that is not allowed in this study, you may be instructed to stop the study treatment but continue to be followed in the study.

11. What happens when the study stops?
If the study is discontinued during your participation, your study doctor will explain the reason and advise you on options for continuing care.

If you are withdrawn from the study during the study treatment period, your study doctor will still need to complete any required assessments.

If you decide to withdraw consent and stop the study early, please tell your study doctor immediately. You will be asked to return to the study doctor to have final tests completed. Tell the study doctor if you have any side effects for up to 30 days after you stop taking the study drug. He/she may add that information to your study record.

If you withdraw from the study, the Sponsor can use the data collected up to your withdrawal. You can withdraw your permission for the data to be used. However, it will not be possible to delete your data from the results of the completed analyses.

12. Will the study drug be available after I have finished the study?
S-217622 is an experimental drug that can only be given to you for COVID-19 in this research study. As a result, the Sponsor will not continue to provide you with the study drug once you have completed taking part in this study.

13. What if new relevant information becomes available?
You will be told of any new information learned during the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them. As with all studies, if we find out important information that may affect your care, you will be provided with that information.

Sometimes the Sponsor and your study doctor will get new information about the experimental drug being studied. If this happens, your study doctor will tell you about this information and discuss whether you should continue in the study. If you decide not to continue in the study, your study doctor will advise you on your options for continued care. If you decide to continue in the study, your study doctor or study staff will ask you to sign and date a new ICF outlining the discussion.

14. Will I receive any payment for taking part in the study?
You will receive $XX for each completed study visit.

OR
You will not be paid for taking part in this study. However, you will be reimbursed for reasonable expenses incurred for travel to and from the clinic (please present your receipts to the study doctor).

[For US study sites]

Payment received as a research participant may be taxable income to you. If payment is more than $600.00 in a calendar year, the study clinic is required to report this to the Internal Revenue Service (IRS). An IRS Form 1099 (Miscellaneous Income) will be sent to you and a copy will be sent to the IRS.

15. Will it cost me anything to be in the study?

All medications, tests, examinations, and procedures needed only for the study including the study drugs will be provided at no cost to you. The study will not supply or pay for medications you take to treat the symptoms of COVID-19 infection.

If you have received medical care unrelated to the study and such medical care includes the cost of your hospitalization and the cost of any procedure, you or your insurance will be responsible for the cost of that medical care. Since some insurance companies will not cover costs when you are in a clinical study, you will need to call your insurance company and make sure your insurance coverage is not affected by your participation in this study.

16. What if something goes wrong?

To help keep you safe during the study, it is very important you follow all study directions. If you have any unusual symptoms or believe you have an illness or injury that you think could be related to this study, please contact your study doctor or study staff immediately at the phone number listed on the first page of this ICF to be provided with the appropriate treatment or advice. If you believe you need urgent medical attention, please go to your nearest emergency room, or call 911. If you see another medical provider during the study, please inform him/her that you are taking part in this research study.

In case of study-related injury:
[For countries other than the US]
The Sponsor (Shionogi) has insurance to cover all persons participating in this research study. You may be eligible for compensation for any pain and suffering or other losses directly following from your taking part in this research study if the injury or health problems went beyond those identified in this ICF. The Sponsor may not pay if the Sponsor and the study doctor do not agree that your injury resulted from your taking part in this study. You will not be compensated for damages happening as a result of the normal progression of your disease, or for any injury or complication due to a medical condition you already have. The Sponsor may not pay you compensation if you do not follow instructions in the study, take the study drugs incorrectly, or if the law limits the Sponsor's legal responsibility. If you have a study-related injury your study doctor will decide what medical care you need. The U.S. NIH does not have a mechanism to provide direct compensation for research related injury.
[For the US]
The Sponsor (Shionogi) will cover the reasonable medical expenses necessary to treat an illness or injury that occurred as a direct result of your use of the study drug or a test performed only for the purposes of the study, so long as the study procedures have been followed. The Sponsor may not pay if the Sponsor and the study doctor do not agree that your injury resulted from your taking part in this study. Unless you are covered by Medicare, this payment by the Sponsor applies only to costs that are not covered by your health insurance policy or by any other third party. If you are covered by Medicare, the Sponsor will pay the costs of the medical care related to these injuries. There are no plans for payment for lost wages or other expenses. The US NIH does not have a mechanism to provide direct compensation for research related injury.

Due to the coronavirus public health crisis, the federal government issued a Declaration under the Public Readiness and Emergency Preparedness (PREP) Act. This Declaration limits the legal rights of a participant participating in a COVID-19 clinical study that uses a drug, device or vaccine designed to treat, diagnose, cure, or prevent COVID-19. This includes the study drug, S-217622 used in this study. If the Declaration applies, participants using S-217622 in this study will have limits on their right to sue and recover for losses from the researchers, study staff, study doctors or other healthcare providers, study sponsors, manufacturers, or distributors involved with the study, including the University of California. However, the federal government has a program that may provide compensation to you or your family for certain claims if you experience serious physical injuries or death and these costs are not covered by other payors. To find out more about this "Countermeasures Injury Compensation Program" go to https://www.hrsa.gov/cicp/about/index.html or call 1-855-266-2427.

[For US sites/participants]
Federal law requires the Sponsor to inform the Centers for Medicare & Medicaid Services (the agency responsible for administration of the Medicare program) when the Sponsor is going to pay for treatment of an injury to a Medicare beneficiary. The Sponsor or its representatives may need to collect certain personal information about you such as your name, date of birth, gender, social security number, and Medicare ID number (if you have one). The Sponsor needs this information in order to comply with a Medicare reporting obligation. This information may be collected directly from you, or from researchers, physicians, or other healthcare providers who treated your problem or injury. This information and also information about your injury or other

health problem may be shared with others, including Sponsor representatives, Sponsor's insurance company, and the Centers for Medicare & Medicaid Services.

Legal rights
Nothing in this ICF limits or excludes any of your legal rights or remedies or releases the study doctor, Sponsor, or healthcare institution from liability arising out of their negligence.

17. How will my personal information be protected?
This study may only be performed by collecting, using, and sharing the personal information of study participants as described in this ICF and you may therefore only participate in this study if you agree to this.

[Select either OPTION A or OPTION B below.
- Use OPTION A for hospital sites in the European Union (where GDPR applies).
- Use OPTION B for sites in countries outside the EU where there is not a concept of "data controller"].

[OPTION A: The study Sponsor (Shionogi) will be a data controller of the personal information about you that is collected and used for the study. This means we will be responsible for looking after your personal information and using it properly. Your hospital (INSERT NAME) will have a similar responsibility with respect to use of your existing medical records.]
[OPTION B: The study Sponsor (Shionogi) will be responsible for looking after the personal information about you that is collected and used for the study and for using it properly. Your hospital (INSERT NAME) will have a similar responsibility with respect to use of your existing medical records.] [INCLUDE FOR US SITES: In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.] The US government has issued a privacy rule to protect the privacy rights of patients. This rule was issued under a law called the "Health Insurance Portability and Accountability Act" of 1996 (HIPAA) and describes how PHI may be used, disclosed (shared), and made accessible to you. This privacy rule is designed to protect the confidentiality of PHI. Because of the research goals of this study, your study records cannot be kept completely confidential. The following sections provide a specific description of how your PHI will be used and disclosed if you take part in this research study. If you decide to take part in the study, you will be asked to authorize (allow) those uses and disclosures by signing this Authorization. If you choose not to allow these uses and sharing of your PHI, you will not be able to take part in the study.]

The study doctor or study staff will collect certain personal information about you that will be held by your hospital. This includes your name, contact details, other specific identifiers, and health data collected from your existing medical records and collected during the study ("**study**

data"). No more personal information about you will be collected than is necessary to undertake the study.

Your medical records are protected as confidential by law, and your permission is needed for them to be accessed and used for the study. They may be looked at by selected individuals from the study Sponsor, the US FDA, AIDS Clinical Trials Group (ACTG), OHRP auditors, study monitors, other local, US, and international regulatory entities, government authorities, IECs, and IRBs. [INCLUDE FOR US SITES: These include the FDA, the ACTG (the group of researchers from the National Institute of Allergy and Infectious Diseases that is coordinating this study), the OHRP, or other local, US, and international regulatory entities as part of their duties. They may also be viewed by the IRB (a committee that protects the rights and safety of participants in research), NIH, study staff, study monitors, drug companies supporting this study, and their designees.] This is to monitor the study to check that it is being performed in compliance with legal obligations and your rights are safeguarded, and to improve public health by ensuring high standards of drug safety and reliability. Your medical records may be stored in or transferred to a data server, and remotely inspected by the study Sponsor, auditors, study monitors other local, US, and international regulatory entities, government authorities, IECs, and IRBs, but even in these cases each party who sees your information will be obliged to keep it confidential. and use it only for legitimate business, research, regulatory, and commercial purposes.

Before the study doctor shares your study data with the study Sponsor, it will be coded. This means your name will be replaced with a coded reference number (participant ID). The study doctor and your hospital will keep the code list linking your name to the coded reference number confidential. The code list will not be shared with the study Sponsor.

The study Sponsor may share the coded study data with selected individuals from the Sponsor's company, its group companies, its vendors, and partners, and/or other local, US, and international regulatory entities.

With your consent, the study Sponsor will use your coded study data for scientific research purposes, including to carry out and evaluate this study, to understand the study drug and the condition, and advance scientific research and medical discovery.

The study Sponsor will also use your coded study data to meet its legal obligations, for example, in relation to clinical trials and the safety of its products, to seek approval to market its medicines and to inform decisions from regulatory authorities on access and reimbursement of new treatments for the benefit of patients.

For the purposes described above, the study Sponsor may transfer the coded study data to its affiliates, vendors and partners located in other countries which may not be regarded as providing the same level of protection to personal information as the laws of your home country (such as the US, Japan, the United Kingdom, and the Netherlands). The study Sponsor will ensure that adequate safeguards are implemented to protect your coded data, as required under applicable data protection legislation. [ADD NEXT SENTENCE TO ICFs FOR EU SITES] [Where your coded data is being transferred from inside the European Union to outside, such adequate safeguards will include signing the European Commission's Standard Contractual Clauses.]

All information collected about you as part of the study will be sent securely to the ACTG statistical and data management center in the US for combining with information from other study participants and statistical analysis of study results. Your name and other personal identifiers will not be sent. Your research site is responsible for sending your information in accordance with the laws, regulations and policies of your country and research site.

You have certain rights with respect to your study data, such as the right to access, change, delete and restrict or oppose further processing. However, under applicable law these rights may be limited in order to comply with clinical trial regulations or to preserve the scientific usefulness of the data. If you wish to exercise your rights, please contact the study doctor, or study staff.

If you withdraw from the study, your hospital will not collect any further information about you for the purposes of the study. However, your coded study data that has already been collected and shared with the study Sponsor will be kept in connection with the study and used in accordance with the protocol, law, and this consent form.

The hospital will keep the code list and the study data for at least 25 years after the study has ended OR INSERT TIMEFRAME REQUIRED BY NATIONAL LEGISLATION. At the end of the study, the study Sponsor will archive the coded study data for the same duration or longer (for example, when used in applications for marketing approval of new products).

If you have questions, comments, or concerns about how your personal information is being handled in this study, [ADD THIS PHRASE FOR SBV EU SITES: or you wish to obtain a copy of the Standard Contractual Clauses referred to above,] you should contact [the study doctor]/[OR INSERT FOR SBV EU SITES the hospital's Data Protection Officer (DPO) in the first instance.

The DPO for your hospital is [INSERT NAME] and you can contact them at [email] or [Telephone] or by post to [insert address].] They will coordinate with the study Sponsor as necessary.

If your concerns are not resolved [INSERT FOR EU SITES: by the DPO of your hospital,] you may also raise your concerns with [insert relevant national data protection authority]. You can contact them by [insert contact details or website link].

Clinical trials require people working on behalf of the study Sponsor called study monitors to visit the study site and "monitor" (review) how the study is being carried out. The purpose of this review is to make sure that parts of the study are being done according the study assessments as described under Section 5, such as the appropriate data is being collected and recorded from the participants; the study drug is being stored and used according to the study protocol; the study assessments have been done at the times specified in the study plan, etc.
The study monitor also verifies that the data has been correctly noted or entered into the study records. This is called "data verification".

In this study, study monitors will be verifying certain data without visiting the study sites. You are being requested to allow the study monitors to view and verify your data and health records collected during this study through electronic means from a remote/distant location.

Your medical files may also be reviewed remotely (outside of the study site) in order to check the information and verify the clinical study procedures, without breaking your confidentiality. If

your medical files are reviewed remotely, the records will include your participant ID number but will not include your name or other directly identifiable information, unless these records will be reviewed <directly through the study site's secure electronic medical records portal or through other secure viewing platform where permitted by local regulations and health authority guidance.>

Whether your medical files are reviewed at the study site or remotely for the purposes of the study, your records will be kept secure during this process.

Remote and digital reviews may be adopted to allow the study monitors to remotely review the study information. Such reviews will involve health records collected for the study and discussed in new ways. These reviews may include the following:

- Information from your health records may be "redacted" by the study staff and forwarded by email, fax, or secure portal to remote-based study monitors, auditors, and other individuals. "Redacted" means that your identifying information will be removed and replaced with your participant ID.
- The study staff may provide study monitors, auditors, and other individuals with secure remote access to their electronic systems.
- Certain sections from your health records may be shared by the study staff with the study monitors, auditors, and other individuals using televisit technology (live video).
  In all cases, the study staff and the study monitors, auditors, and other individuals (as explained in [Section 16] will implement technical and organizational controls to ensure that your confidential personal information is protected from unauthorized access or loss.

18. At the end of the study, where are the summary results posted and how will the coded study data be shared for future scientific research?

Information about this study and result summaries will be publicly available on the website of "SHIONOGI CLINICAL TRIAL DATA":
http://www.shionogi.co.jp/en/company/development/clinical-trial.html /
http://www.shionogi.co.jp/company/development/clinical-trial.html (Japanese)
and the following clinical trial registries: EU Clinical Trials Register:
https://www.clinicaltrialsregister.eu; Japan Clinical Trials Register: https://www.clinicaltrials.jp or https:/umin.ac.jp/ctr/index-j.htm.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

This information is disclosed to other national clinical trial registries or databases according to industry guidance and regulatory requirements. You can search the website or these public registries any time. You will not be able to be identified from any summary results, reports, or publications produced at the end of the study. At the end of the study, the study Sponsor may make coded participant-level study data available to qualified researchers for approved future scientific research to be conducted in your country or abroad. The researchers may belong to the study Sponsor's group companies or to independent third parties such as publicly funded healthcare bodies, universities, and/or pharmaceutical companies. Where possible, the study Sponsor will anonymize the coded study data before it is shared securely for future scientific

research. Data sharing requests will be subject to formal approval processes and safeguards will be put in place to control access and protect your privacy.

The responsible sharing of clinical trial research data for future scientific research maximizes the value of the data and helps to advance scientific knowledge and public health. The data will be used for future scientific research only and will not be used to make future decisions about your healthcare. If you do not want your coded study data to be used for future scientific research, you can object to this at any time by notifying the study doctor. However, in some cases, national laws may restrict that right to preserve the scientific integrity of the data. If you object, your coded study data will not be used for further scientific research, but this will not affect any research activities already undertaken.

19. Who has reviewed this study?

An IEC/IRB is a group of scientific and non-scientific people who perform the initial and ongoing ethical review of the clinical study with the research participant's rights and welfare in mind. This study has been reviewed and approved by an IEC/IRB ([name of IEC/IRB]) and the [country] Health Authority.

20. Further information and contact details

If you have questions, concerns, or complaints about this study or to report a study-related injury, contact your study team listed below:

	Study Doctor	Study Coordinator
Name:		
Telephone number:		
24-hour contact number(s):		

If you have any questions or concerns about your rights as a research participant or want to discuss a problem, get information, or offer input, you may contact the IEC/IRB at [insert phone number].

Thank you for reading this and considering taking part in this study.

If you decide to take part, you will receive a copy of this signed and dated Informed Consent Form to keep.

[Country specific requirements should be included.]

- For the US, use "legally authorized representative" instead of "legally acceptable representative".
- Checkboxes may be deleted depending on the country.

SIGNATURE FORM

Protocol Title: A Phase 3, multicenter, randomized, double-blind, 24-week study of the clinical and antiviral effect of S-217622 compared with placebo in non-hospitalized participants with COVID-19

Product Name: S-217622

Study Phase: Phase 3

Study Doctor: Investigator name, address and phone number including area code

To consent to participating in the above study, please read each statement and if you agree mark each check box YES, then sign below.

This consent form contains important information. It will help you decide if you want to take part in this study. If you still have questions, please ask the study doctor or one of the study staff, before signing and dating this form.

1. I confirm that the study has been explained to me and that I have read the informed consent for the above study. I have had sufficient time to consider the information, ask questions, and have had these answered satisfactorily.
☐ Yes
☐ No

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
☐ Yes
☐ No

3. I give my permission to the study doctor and study staff for my medical records to be accessed by selected individuals from the study Sponsor, auditors, study monitors, other local, US, and international regulatory entities, government authorities, IECs, and IRBs for monitoring purposes.
☐ Yes
☐ No

4. I give my permission for my coded study data to be collected, used, and shared as explained in this informed consent form.
☐ Yes
☐ No

I understand that:
- I cannot participate in the study if I do not agree to this or if I withdraw my consent.
- My coded study data may be shared (where possible in anonymized form) with qualified researchers for approved future scientific research and subject to any legal restrictions, I can object to this by contacting the study doctor.

5. *Sites: [modify per local requirements for obtaining health care* records.]

With your permission, for which you may need to sign a separate form, study staff may contact your health care provider or hospital(s) where you might receive care to determine if you have been hospitalized, received outside treatment for COVID-19 infection, or died while in the study, and the cause of death. The study team may also want to discuss the medicines you are currently taking and if they can be safely stopped, if necessary, during the study. You can still participate in this study even if you do not give us permission to contact your health care provider or hospital(s).

☐ **Yes,** I agree ☐ **No,** I do not agree

6. I confirm that I have not been pressured by the study doctor or study staff to be in this study. ☐ Yes ☐ No

7. I understand that I cannot be in another treatment study while I am in this study, unless I am hospitalized for COVID-19 ☐ Yes ☐ No

8. I understand that I may receive S-217622 or placebo (the placebo looks like S-217622 and is given in the same way, but it has no active ingredient in it). ☐ Yes ☐ No

9. I agree to take part in the above study. ☐ Yes ☐ No

10. I have been told about locally available COVID-19 treatment that may be available to as an alternative to study participation. ☐ Yes ☐ No

You will receive a copy of this signed and dated Signature Form; 1 original will be kept in medical notes and 1 copy will be placed in study site file.

Printed name of participant, in full

Signature of participant Date (dd-MON-yyyy)

Printed name of person obtaining consent

Signature of person obtaining consent Date (dd-MON-yyyy)

Printed name of Study Doctor if different from the person obtaining consent

Signature of Study Doctor if different from the person obtaining consent	Date (dd-MON-yyyy)

(If it applies) I confirm as the Legally Acceptable Representative that the information in this Informed Consent Form has been explained and is understood by the subject for the above study. The subject has had sufficient time to consider the information, ask questions and have had these answered satisfactorily.

Printed name of legally acceptable representative (if appropriate)	
Signature of legally acceptable representative	Date (dd-MON-yyyy)
Relationship of legally acceptable representative to the participant	
Printed name of witness (if appropriate)	
Signature of witness (if appropriate)	Date (dd-MON-yyyy)
Relationship of witness to the participant (if appropriate)	

HIPAA Authorization to Use and Disclose Protected Health Information (For US only)

The US government has issued a privacy rule to protect the privacy rights of patients. This rule was issued under a law called the "Health Insurance Portability and Accountability Act" of 1996 (HIPAA) and describes how PHI may be used, disclosed (shared), and made accessible to you. This privacy rule is designed to protect the confidentiality of PHI. Please read this Authorization carefully, as it describes your rights regarding the use or disclosure of your PHI.

You are being asked to allow the use of your PHI because this study may be performed only by collecting and using this information. Your study records will be kept confidential as described in this form. Only a number and initials will be used to identify you in the study data sent to others, and you will not be personally identified in any reports or publications that may result from this clinical study. The information about you that will be reviewed by the study doctor and study staff for the study may allow you to be identified by your name, address, telephone number, social security number, health plan number, study number, date of birth, dates relating to various (different) medical surgeries, or other identifying information.

Because of the research goals of this study, your study records cannot be kept completely confidential. The following sections provide a specific description of how your PHI will be used and disclosed if you take part in this research study. If you decide to take part in the study, you will be asked to authorize (allow) those uses and disclosures by signing this Authorization. If you choose not to allow these uses and sharing of your PHI, you will not be able to take part in the study.

Information that may be given to others by the study doctor and/or study staff:

- Past and present medical records
- Research records, including records of study visits and phone calls about the study
- Information collected for this study from:
    - Physical exams
    - Laboratory and other test results, including tests for reportable infectious diseases
    - Study questionnaires
    - Records about the study drug you received
    - Records about the diagnosis and treatment of any mental health condition(s)
    - Information about your (or your partner's) pregnancy and its outcome, should you (or your partner) get pregnant during participation in the study

Your information may be used or shared with others for the following purposes:

- To conduct and oversee research
- To support the development and testing of the investigational rapid diagnostic tests that may be used in the study
- To ensure the research meets legal, institutional, and accreditation requirements
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm)
- To perform future research
- Researchers may need to discuss your health care with your regular physician when

appropriate to maintain the quality of your treatment
- When required by law
- To make sure the research was performed correctly

For the purposes described immediately above, your information may be shared with:
- The Sponsor and its representatives and vendors providing services for this study
- Outside individuals or entities that have a need to access this information to perform functions on behalf of the hospital and its affiliates, for example, data storage companies, insurers, or legal advisors
- Other research doctors and medical centers participating in this research or in your treatment outside the study
- The US FDA
- The Department of Health and Human Services (DHHS)
- Other federal and state agencies and government agencies in other countries
- IEC or IRB overseeing this study
- Hospital accrediting agencies

Your anonymized data may be shared with certain vendors and/or other researchers for the purpose of conducting future or additional research focused on the improvement of public health and the advancement of science and medicine. However, once your study information is shared as authorized, it may no longer be protected by federal law and there is a chance it may be re-disclosed without your permission. The Sponsor will ensure that those vendors and/or researchers are required to hold your information as confidential.

If you do not give permission to use and give out your health information, you will not be able to take part in this study. While the study is in progress, you will not have access to your study records. You will be able to access your information when the clinical study is completed. After the study is completed, you have the right to see and copy the health information collected from you during the course of the study for as long as that information is maintained (kept) by the study staff and other entities according to federal privacy regulation (law). You have the right to request corrections of incorrect data (information) if needed.

You may withdraw your permission for us to use and give out your health information at any time. To do this, a written withdrawal notice must be submitted to your study doctor at the following address:

«FirstName»«MiddleName»«LastName»«Suffix»
«Company»
«Address»«SuiteDept»
«City»«State»«Zip»

If you withdraw from the study and withdraw your Authorization, no new information will be collected for study purposes unless the information concerns an adverse event (a bad effect) related to the study. If an adverse event occurs, your entire medical record may be reviewed. All information that has already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the Sponsor.

If you withdraw your Authorization, you will not be able to stay in the study. After you withdraw your Authorization, no new health information identifying you will be gathered. However, information already gathered may be used and given to others. If you withdraw from the study but do not withdraw your Authorization, new personal health information may be collected until this study ends.

This Authorization does not have an expiration date. If you do not withdraw this Authorization in writing, it will remain in effect indefinitely. [FOR SITES IN CALIFORNIA AND WASHINGTON, PLEASE REPLACE THE PREVIOUS TWO SENTENCES WITH THE FOLLOWING LANGUAGE: This Authorization will expire 31 December 2050, unless you withdraw it in writing before then.

Your study doctor will keep this Authorization for at least 6 years.

If you do not sign this Authorization, you cannot take part in this clinical study or receive study-related treatment. If you withdraw this Authorization while you are in the study, you will no longer be able to take part in this study. Your decision to withdraw your Authorization, or not to take part in the study, will not involve any penalty or loss of access to treatment or other benefits to which you are entitled.

AUTHORIZATION

By signing this Authorization, I give permission to [name or other identification of specific healthcare provider(s) or description of classes or persons, (e.g., all doctors, all healthcare providers)] at [name of covered entity or entities] to use or disclose (release) my PHI as explained above. I have been told that I will receive a signed and dated copy of this Authorization for my records.

Printed Name of Participant

Signature of Participant **Date (dd-MON-yyyy)**

OR

By signing this Authorization, I give permission to [name or other identification of specific healthcare provider(s) or description of classes or persons (e.g., all doctors, all healthcare providers)] at [name of covered entity or entities] to use or disclose (release) participant's PHI as explained above. I have been told that I will receive a signed and dated copy of this Authorization for my records.

Printed Name of Participant

Printed Name of Legally Authorized Representative

Signature of Legally Authorized Representative **Date (dd-MON-yyyy)**

Following section to be completed by person obtaining Informed Consent:

Printed Name of Person Obtaining Authorization

Signature of Person Obtaining Authorization **Date (dd-MON-yyyy)**