Phase II, Randomized, Investigator Initiated Trial to Evaluate Safety and to Explore Clinical Benefit of Silmitasertib (CX-4945) in Patients With Severe Coronavirus Disease 2019 (COVID-19)

Informed Consent Form

NCT04668209

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Consent to Participate in Research

Study Title: **A Phase II, Randomized, Investigator Initiated Trial to Evaluate Safety and to Explore Clinical Benefit of Silmitasertib (CX-4945) in Patients with Severe Coronavirus Disease 2019 (COVID-19)**

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Summary of the research:

This is a consent form for participation in a research study. Your participation in this research study is voluntary. This consent form contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to ask questions before making your decision whether or not to participate.

Coronavirus Disease 2019 (COVID-19) is a respiratory illness that can spread from person to person. The infectious agent that causes COVID-19 is a novel coronavirus (named SARS-CoV-2). It was first identified during a recent outbreak in December 2019 in Wuhan, China. Patients with COVID-19 have had mild to severe respiratory illness with symptoms of fever, cough, and shortness of breath along with non-specific symptoms including myalgia (muscle pain) and fatigue. Some patients were more likely to develop a severe respiratory illness similar to severe acute respiratory syndrome (SARS) or even die from the disease.

The current standard of care treatment includes oxygen therapy. There is no specific antiviral treatment recommended for COVID-19 by the Centers for Disease Control and Prevention (CDC). Patients with COVID-19 should receive supportive care to help relieve symptoms. For severe cases, treatment should include support for vital organ functions.

Silmitasertib is a first-in-class small molecule drug that targets a protein, Casein Kinase 2 (CK2). Researchers have identified CK2 as a possible target for the treatment of COVID-19. Dysregulation (hyperstimulation) of CK2 can indirectly contribute to successful viral replication and development of a cytokine storm. A cytokine storm is an over-activation of white blood cells, which releases too many cytokines (inflammation-stimulating molecules) into the blood and is often associated with a surge of activated immune cells into the lungs. This can lead to acute respiratory distress syndrome (ARDS).

In ARDS, fluid builds up in the alveoli (tiny, elastic air sacs in your lungs). The fluid keeps your lungs from filling with enough air which means less oxygen reaches your bloodstream. This deprives your organs of the oxygen they need to function. ARDS is known to be one of the main reasons for death in patients with COVID-19. Researchers noted that by inhibiting CK2, COVID-19's cellular environment could potentially shift into a more antiviral state.

The University receives compensation from the sponsor of this study for the conduct of this study. If you have any questions, please discuss this with your study doctor. Senhwa Biosciences, Inc. will be providing Silmitasertib for this research study.

Why is this study being done?

You are being asked to participate in this research study because you have contracted severe COVID-19. This is a research study to test a new investigational drug, Silmitasertib. An investigational drug is one that has not been approved by the United States Food and Drug Administration (FDA).

The purpose of this research study is to test the safety and effectiveness of Silmitasertib in severe COVID-19 patients.

What will happen if I take part in this study?

Screening Visit:

After signing this consent document, the study will begin with a screening visit. The purpose of the screening visit is to find out if you meet all of the requirements to take part in this research study. The procedures and assessments that will be completed during screening are listed in the table below.

These assessments must take place within 7 days before you receive your first dose. It is possible that after the screening tests are reviewed, you will not be able to take part in this study. If you do not meet the requirements, the study doctor will explain why and will discuss with you other treatment options, if available.

Treatment Phase:

If you pass the screening tests, you will be randomly assigned to one of two groups to receive Silmitasertib (CX-4945) plus standard treatments for COVID-19 and your symptoms, or to receive standard treatments alone. You have an equal chance (50/50) of being assigned to one of the groups.

If assigned, you will take Silmitasertib pills twice a day, by mouth and with only water. The treatment phase can last up to 14 days.

You will take five 200-mg pills twice daily, two hours after the morning meal and two hours after the evening meal (dinner). Patients are advised to take 1 capsule at a time with a glass of water. You may pause in between swallowing each pill and can take up to 10 minutes to swallow all 5 pills.

You will be instructed to take another medication by mouth 1 hour prior to taking the pills. This medication may help prevent you from feeling sick (nauseous) after taking Silmitasertib.

If you recover while on Silmitasertib to the point of discharge, it is at the treating physician's discretion to take you off the study drug or have you continue the study drug at home. In the case that the treating physician decides to keep you on Silmitasertib after discharge, you will be provided with written instructions and a diary to keep track of when to take it.

If you are discharged from the hospital prior to day 14, you may be required to return to the clinic for an in-person visit at Days: 8, 11, and 14. The visit will include procedures listed below in the table.

Follow Phase:

Once your treatment is stopped, three follow-up visits will occur on Days 28, 45, and Day 60. Follow-up visits may be completed via phone or telehealth, if your doctor thinks it is safe.

Your study coordinator will call you every day through at least Day 28 to ask you questions about your health status and check your medical records for new information. These calls will take about 5 minutes or less and will occur even if you are discharged or the study treatment is discontinued.

The procedures and assessments that will be required during the study are listed in the table below. In addition to the visits listed, your research study doctor may ask you to come in for an extra visit, if necessary, to protect your well-being.

Please let your study coordinator the best method to contact you to collect follow up information (telehealth visits, outpatient clinic, telephone calls, texts, and email). They will do the best they can to reach you during the follow up period.

Procedure/Assessments	Screening Visit	Treatment Phase					Follow-Up***		
Day	SV	Day 1 (Baseline)	Day 4	Day 8	Day 11	Day 14/ EOT	Day 28	Day 45	Day 60
Informed Consent	X								
Medical History & Demographics	X								
Physical Examination	X	X		X		X	X	X	
Measuring vital signs	X	X	X	X	X	X	X	X	
Patient Questionnaire (EQ-D5-5L)		X		X		X	X		
Assessment of your clinical status/ recovery**	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram (ECG)	X					X			
Blood sample for safety tests	X	X	X	X	X	X	X	X	
Pregnancy Test (females who can have children)	X					X			
Urine sample	X	X	X	X	X	X	X	X	
Blood sample to check your response to treatment		X	X	X	X	X			
Nasal swab to check for virus*	X	X		X		X	X		
Chest scan to measure disease in your lungs*	X	Day 5, Day 14 if recommended by your doctor							
Treatment Assignment		X							
Silmitasertib (CX-4945) treatment and necessary co-medicines		CX-4945 (1000mg/ 5 pills), by mouth, twice a day, on Days 1 - 14							
Ask about medications you are taking	X	X	X	X	X	X	X		
Ask about how you are feeling		X	X	X	X	X	X	X	X

*Nasal Swab and Chest scans will be performed if clinically indicated by treating physician.

**phone call daily for at least 28 days, regardless of discharge or treatment discontinuation.

***Follow-up continues after discharge via approaches available to the site staff (e.g., telehealth visits, COVID-19 outpatient clinic, telephone calls, texts, and emails).

How long will I be in this study?

The total duration of the treatment will be 14 days. Patients will be followed up at 28, 45, and 60 days from the start of the treatment. The total duration for each patient in the study (including screening) will be up to 67 days.

How many people will take part in this study?

About 40 patients will participate in this study.

What benefits can I expect from being in this study?

You may or may not benefit as a result of your participation in this study. There is, however, no guarantee that you will benefit from your participation in this study. Information learned from the study may help other people in the future.

What risks, side effects or discomforts can I expect from being in the study?

Taking part in this study involves some risks and possible discomforts. As with any clinical trial, adverse side effects, complications, and/or injury, both expected and unexpected, are possible. While on the study, you are at risk for these effects. There may be risks or side effects with the investigational study drug, Silmitasertib, which are currently unknown. These may be serious, permanent, or even life-threatening. Your condition could worsen while receiving this treatment. You should discuss this with the study doctor.

Approximately 75 patients with solid tumors have already been treated with Silmitasertib capsules as a single agent in an earlier cancer clinical trial, receiving the medication either twice-daily or four times daily. In general, more drug-related adverse reactions were reported when patients took Silmitasertib four times daily, and that is why this study will only dose patients twice daily.

The most frequently reported drug-related reactions when Silmitasertib was used as a single agent were gastrointestinal disorders (75%) such as diarrhea, nausea, and vomiting, etc. The metabolism and nutrition disorders were 35.3% such as hypokalemia (low potassium), and the general disorders were 26.9% such as fatigue. Nervous system disorders were 11.9% such as dizziness and headache.

You may experience some temporary changes in the laboratory result that measure the function of your liver (the organ that aids in digestion and the removal of waste products). In a study of Silmitasertib in combination with gemcitabine and cisplatin in cholangiocarcinoma (bile duct cancer) patients, there have been two deaths of patients while on the study or within 30 days after the last dose that were possibly related to Silmitasertib.

You may also experience some temporary changes in laboratory tests that measure the function of your kidneys (the organs that excrete waste products and maintain the balance of body fluids) or blood electrolytes imbalance (the salts that usually circulate in your blood), and tiredness. Some of the reports of diarrhea and blood electrolyte imbalance have been severe so you must take medicines as prescribed by your study doctor to prevent and treat nausea, vomiting, and diarrhea. Throughout your participation in this study, your blood will be tested regularly during your clinic visits to follow the effects Silmitasertib may have on the function of these organs.

You should discuss your concerns with your study doctor. Let your study doctor know about the side effects that you are experiencing. Your study doctor may be able to give you other drugs to treat and make side effects less severe or less uncomfortable. Many side effects go away

after the Silmitasertib regimen has been stopped, but in some cases these side effects may be serious and/or long lasting. In rare cases, side effects could be fatal.

We do not know how well Silmitasertib capsules combine with alcohol or with other drugs. You should always discuss the use of alcohol or any other drugs (including over-the-counter, prescription, illegal, or herbal) with the study doctor while you are participating in this study.

RISKS OF STUDY PROCEDURES

- Electrocardiogram (ECG, a measure of the heart's rhythms): Skin irritation is rare but could occur during an ECG from the electrodes or gel that is used.
- Questionnaires: The questionnaires used in this study may be upsetting. You do not need to answer any questions that you are not comfortable with.

UNFORESEEN RISKS

Since Silmitasertib is investigational, there may be other unknown risks. Additionally, there may be unknown risks to a pregnancy, embryo, or fetus if you or your female partner becomes pregnant.

BIRTH CONTROL RESTRICTIONS

Taking Silmitasertib may involve risks to a pregnant woman, an embryo, fetus (unborn baby), or nursing infant. Therefore, if you are pregnant, planning to become pregnant, planning to father a child, or are breastfeeding a child, you cannot participate in this study.

Females

To reduce the risk of pregnancy, you should use an effective method of birth control while you are participating in this study, and for six months after your last dose of Silmitasertib. During the study, the study doctor must confirm the use of two acceptable contraceptive methods, the patient's understanding of the risk of Silmitasertib to an unborn fetus, and documentation of a negative pregnancy test before dispensing Silmitasertib to a woman of childbearing potential. Not all methods of contraception are acceptable. You will have to discuss this in detail with your study doctor or study staff.

If you become pregnant while you are participating in this study or within six months after you have stopped taking Silmitasertib, tell your study doctor or study staff immediately. Silmitasertib will be stopped, and your participation in this study will be ended.

Males

To reduce the risk of pregnancy, you should use an effective method of birth control while you are participating in this study, and for six months after your last dose of Silmitasertib. Acceptable methods of birth control for use in this study will be discussed with the study doctor or study staff.

If your female partner becomes pregnant while you are participating in this study or within six months after you have stopped taking Silmitasertib, tell your study doctor or study staff immediately.

What other choices do I have if I do not take part in this study?

If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The University of Arizona. If you are a student or employee at the University of Arizona, your decision will not affect your grades or employment status.

You do not have to be in this study to receive treatment for severe COVID-19. Your options may include:

- Remdesivir
- Dexamethasone
- Taking part in another study
- Getting other therapy (either experimental or not experimental)

Please talk to the study doctor about your options before you decide whether or not you will take part in this study.

When may participation in the study be stopped?

Your decision to participate in this study is voluntary. You may choose to not participate or you may withdraw from the study for any reason without penalty or loss of benefits to which you are otherwise entitled and without any effect on your future medical care. However, please note that the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study.

If you decide to withdraw from the study, the data that was collected before you withdrew will continue to be part of the study. Once you withdraw from the study, no additional data will be collected about you for the study unless you agree otherwise to have further tests and examination. You can still be in the study if you are taken off the study medication early. This may happen if your doctor thinks it is necessary for your safety. In this case, the same study information will be collected from you and your medical records.

The study doctor can stop your participation at any time without your consent for the following reasons:

- If it appears to be medically harmful to you;
- If you fail to follow directions for participating in the study;
- If it is discovered that you do not meet the study requirements;
- If the study is canceled; or

- For administrative reasons.

If you leave the study for any reason, you will be asked to complete an end of study visit which may include but not limited to physical exam, vital signs, quality of life questionnaire, lab tests, questions about your medications and how you are feeling, and a medical records review. These tests are done as a safety follow up before you exit the study.

What happens if I am injured because I took part in this study?

Side effects (injury) can happen in any research study. These effects may not be your fault or the fault of the researcher involved. Known side effects have been described in this consent form. However, side effects that are not currently known may happen and require care. If you experience an injury or adverse event, please call Dr. Glassberg at (602)521-3400 immediately. If the investigator determines that the injury or adverse event is due to your participation in this research, you will be treated in the hospital with standard of care procedures.

If your condition becomes worse, other sickness develops, or you are injured while you are in the study, get the medical care that you need right away. You should inform the healthcare professional treating you that you are participating in this study. If you tell the study staff that you think you have been injured, then they will help you get the care you need.

If you are injured as a result of taking Silmitasertib, or from procedures done for this study, you will be treated by your doctor according to standard of care.

If you are injured, have an adverse reaction or illness as a direct result of a defect in the manufacture or shipment of the study drug Silmitasertib, Senhwa will pay for the cost of diagnosis and treatment expenses. Senhwa will not pay for any injury, adverse reaction, or illness caused by the study team's failure to correctly perform any procedures. By signing and dating this document, you will not lose any of your legal rights or release anyone involved in the research from responsibility for mistakes.

To pay medical expenses, the study doctor will need to know some information about you like your name, date of birth, and Medicare Beneficiary Identifier (MBI). This is because the study doctor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

The University of Arizona and Banner-University Medical Center have no funds set aside for the payment of treatment expenses for this study.

What are the costs of taking part in this study?

Silmitasertib and required 5HT-3 antagonist (anti-nausea medication) will be provided at no charge to you or your insurance company. There will be no charge to you for procedures

performed for research purposes only while you are participating in this study. Routine medical care performed while participating in study will be billed to you and/or your insurance company. This will include (but is not limited to) physical exam, nasal swabs, laboratory tests, administration of medications (to include Silmitasertib), and the treatment of side effects.

Not all insurance companies are willing to pay for services performed in a clinical trial. You will be responsible for any charges that your insurance does not cover including regular co-payments and deductibles. Please speak with your insurance company to find out what you may be financially liable for.

Will I be paid for taking part in this study?

You will not receive any payment for taking part in this study.

Will my data or specimens be stored for future research?

Your private information or biospecimens collected during this study will not be used or distributed for future research studies not described here, even if identifiers are removed. However, study data may be used for future research not described here (no private information will be included).

Will my specimens be sold for commercial profits?

The information collected as part of this study may be shared with other organizations. You will not share in any commercial value or other compensation from products developed using the information. No private information will be included with any information shared.

Will I hear back on any results that directly impact me?

Research results that are clinically relevant, including individual research results, will not be disclosed to you.

Will Whole Genome Sequencing be done with my specimen?

No, whole genome sequencing will not be done with your specimen.

Will my study-related information be shared, disclosed, and kept confidential?

It is anticipated that there will be circumstances where your study related information and Protected Health Information (PHI) will be released to persons and organizations described in this form. If you sign this form, you give permission to the research team to use and/or disclose your PHI for this study. Your information may be shared or disclosed with others to conduct the study, for regulatory purposes, and to help ensure that the study has been done correctly.

These other groups may include:

- Office for Human Research Protections, Food and Drug Administration, or other federal, state, or international regulatory agencies
- Banner University Medical Group and Banner Health
- The University of Arizona (UA) and the UA Institutional Review Board

- The funder supporting the study, Senhwa Biosciences, Inc, their agents or study monitors
- Your primary care physician or a specialist taking care of your health.

If you agree to take part in this study a copy of this signed informed consent form will be saved into your electronic medical record (EMR) at Banner Health. As a result, healthcare providers and staff who are not working on this study, but who may provide you medical treatment in the future, will know that you are taking part or took part in this study.

Your PHI may no longer be protected under the HIPAA privacy rule once it is disclosed by the research team. While every effort will be made to protect the privacy of your information, absolute confidentiality cannot be guaranteed. This does not limit the duty of the researchers and others to protect your privacy.

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

What study-related information and PHI will be obtained, used or disclosed from my medical record at Banner?

Information related to this research study that identifies you and your PHI will be collected from your past, present, and future hospital and/or other health care provider medical records.

The PHI you are authorizing to be used and/or disclosed in connection with this research study is:

- Name, address, phone number, email address, medical record number
- Demographics, elements of dates
- Medical history
- Clinical status

Demographic information to be disclosed may include, but is not limited to, your name, address, phone number, or social security number. If you receive compensation for participating in this research study, information identifying you may be used or disclosed as necessary to provide that compensation.

Your existing health records may include information related to the diagnosis or treatment of sexually transmitted disease (STD), acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV), other communicable diseases, genetic information (e.g., genetic testing), and/or alcohol and/or drug abuse. The study staff and study sponsor's monitor may see this information while reviewing your regular health records for this study, but they WILL NOT create, collect, or disclose this type of information for the purposes of this research study.

When will my authorization expire?

There is no expiration date or event for your authorization. Therefore, unless you cancel this authorization (as instructed below) this authorization will continue to be effective.

Do I have to sign this authorization form?

You do not have to sign this authorization. However, if you decide not to sign, you will not be able to participate in this research study; and it will not affect any non-study Banner Health medical treatment or health care, payment, enrollment in any health plans, or benefits.

Also, by signing this form you are authorizing and permitting uses and/or disclosures of your PHI for future research purposes (e.g., future studies) as described in this document.

What do I need to know if I decide to cancel my authorization?

After signing the authorization, you may decide to cancel your previous authorization for the research team to use your PHI. If you cancel the authorization, you will no longer be able to stay in the research study. Please note that any PHI collected before you cancel the authorization may still be used. You may revoke the authorization by contacting the Principal Investigator in writing. Contact information is under "Who can answer my questions about the study" at the end of this document.

Will access be limited to my research study record during this study?

You may not have access to the research information developed as part of this study until it is completed.

Who can answer my questions about this study?

If at any time you feel you have had a research-related injury, or for questions, concerns, or complaints about the study you may contact:

Dr. Glassberg and research team at (602)521-3400
Dr. Chaudhary and research team at (520)626-8000

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Human Subjects Protection Program Director at 520-626-8630 or online at http://rgw.arizona.edu/compliance/human-subjects-protection-program.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact:

Dr. Glassberg and research team at (602)521-3400
Dr. Chaudhary and research team at (520)626-8000

If you have questions, concerns, or complaints about the use or sharing of your health information or would like a copy of the Banner Notice of Privacy Practices, you may contact the

Banner Research HIPAA Liaison at 602-839-4583 or BHResearchCompliance@bannerhealth.com.

To cancel your authorization for access to PHI you must notify the *Principal Investigator* and/or *Research Team* in writing at the following address:

Marilyn K. Glassberg, MD and Research Team
Banner University Medical Center Phoenix
Lung Institute
755 East McDowell Road, Third Floor
Phoenix, AZ 85006

Sachin Chaudhary, MD and Research Team
University of Arizona
1515 N. Campbell Avenue
Tucson, AZ 85724

Signing the consent form

I have read (or someone has read to me) this form, and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study and I authorize the use and/or disclosure of my PHI. I am not giving up any legal rights by signing this form. I will be given a signed copy of this form**.**

Printed name of subject	Signature of subject	Date

Printed name of person authorized to consent for subject (when applicable)	Signature of person authorized to consent for subject (when applicable)	Date

Relationship to the subject

Investigator/Research Staff (not applicable if completed electronically)

I have explained the research to the participant or the participant's representative before requesting the signature(s) above. There are no blanks in this document. A signed copy of this form has been given to the participant or to the participant's representative.

Printed name of person obtaining consent	Signature of person obtaining consent	Date

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