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)

Study Protocol and Statistical Analysis Plan

NCT04668209

February 10, 2021

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)

Protocol Number:	**CX4945-AV02-IIT**
Version:	**3.0**
Date:	**01 February 2021**
Study Product:	**Silmitasertib (CX-4945)**

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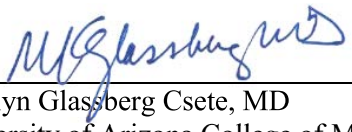
PROTOCOL APPROVAL PAGE

Protocol Number:	**CX4945-AV02-IIT**
Version:	**3.0**
Date:	**01 Feb 2021**

We, the undersigned, have reviewed this protocol and agree that it contains all relevant information required to meet FDA, GCP and all applicable regulatory guidelines and statutes.

PROTOCOL APPROVAL FOR USE



February 10, 2021

Marilyn Glassberg Csete, MD
University of Arizona College of Medicine
Chief of Pulmonary, Critical Care, and Sleep Medicine

Date

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**CX4945-AV02-IIT**
Version:	**3.0**
Date:	**01 February 2021**

I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical trial. I also agree to comply with US Food and Drug Administration (FDA) regulations and Investigational Review Board/Institutional Ethics (IRB/IEC) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met.

Principal Investigator's Signature _____ Date _____

Print Name _____

Site Name _____

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SUMMARY OF SIGNIFICANT CHANGES IN UPDATED CLINICAL PROTOCOL CX4945-AV02-ITT

Version 3, dated 09 February 2021
Replacing Version 2, dated 06November 2020

Section /Topic	Changes Made in Clinical Protocol v#3
Section 1.3 Schedule of Activities, Footnote #16 / Data collection after hospital discharge	***Language Added*:** [16] Patient follow-up should continue after discharge via approaches available to the site staff (e.g., telehealth visits, COVID-19 outpatient clinic, telephone calls, texts, and emails to the patient and close contacts).
Section 5.1 Patient Eligibility Confirmation/ Inclusion Criteria	***Administrative Change:*** Inclusion Criteria #2 shall read that a positive COVID-19 test is required within 7 days of randomization, either original diagnosis or a confirmation test. ***Administrative Change:*** Patient shall meet inclusion criteria #3 if the require ≥ 2L oxygen in order to normalize SaO2. An adequate SaO2 does not need to be maintained for the patient to qualify ***Revision:*** Inclusion criteria #6 was revised to read that a patient meets eligibility in the absence of any active or recurring clinically significant hepatic disease' and with a Albumin level of ≥2.5 g/dL
Section 8.1 Study Procedures/ Preventing Missing Data	***Language Added:*** Patient follow-up should continue after discharge via approaches available to the site staff (e.g., telehealth visits, COVID-19 outpatient clinic, telephone calls, texts, and emails to the patient and close contacts). These efforts should prevent missing data while limiting additional public health risks and unnecessary community exposure.

1. PROTOCOL SUMMARY

1.1. SYNOPSIS

<table>
<tr><td>Title:</td><td>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)</td></tr>
<tr><td>Study Description:</td><td>COVID-19 is characterized by SARS-COV-2-induced upregulation of host protein kinase CK2 that catalyzes phosphorylation of many proteins, modulating their activities in cellular processes. SARS-COV-2 nucleocapsid directly targets CK2 and this viral-host protein interaction affect many vital processes in host cells contributing to dysregulated host immune response, viral survival, replication and spread to nearby cells. Silmitasertib demonstrated anti-viral and anti-inflammatory efficacy in COVID-19 in vitro studies and remarkable clinical benefits under emergency IND authorization

This multi-center, open-label, 2 arm parallel-group, randomized, interventional prospective exploratory study in 40 patients aimed to evaluate safety and explore putative clinical benefits of Silmitasertib 1000 mg BID dose in patients with severe illness caused be SARS-COV-2. This will be a two-arm trial comparing the SOC/best supportive care alone to the SOC/best supportive care with addition of Silmitasertib (allocation ratio 1:1).</td></tr>
<tr><td>Primary Objective and Endpoints:</td><td>
<table>
<tr><th>Primary Objective</th><th>Primary Endpoint</th></tr>
<tr><td>To assess safety and tolerability of CX-4945 administered orally twice daily to patients with severe COVID-19</td><td>Adverse Events experienced by the patients from randomization to Day 60 (including vital signs, physical findings, clinical laboratory, and ECG results) as characterized by type, frequency, severity (as graded by Common Terminology Criteria for Adverse Events (CTCAE version 5.0), timing, seriousness, and relationship to study therapy.</td></tr>
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</td></tr>
<tr><td>Secondary Objectives and Endpoints:</td><td>
<table>
<tr><th>Secondary Objectives</th><th>Secondary Endpoints</th></tr>
<tr><td>To compare time to clinical recovery in CX-4945 treatment group evaluated from</td><td>• Number of days from randomization to discharge, or to alleviation of cough (defined as mild or absent in a patient reported scale of 0=absent, 1=mild,</td></tr>
</table>
</td></tr>
</table>

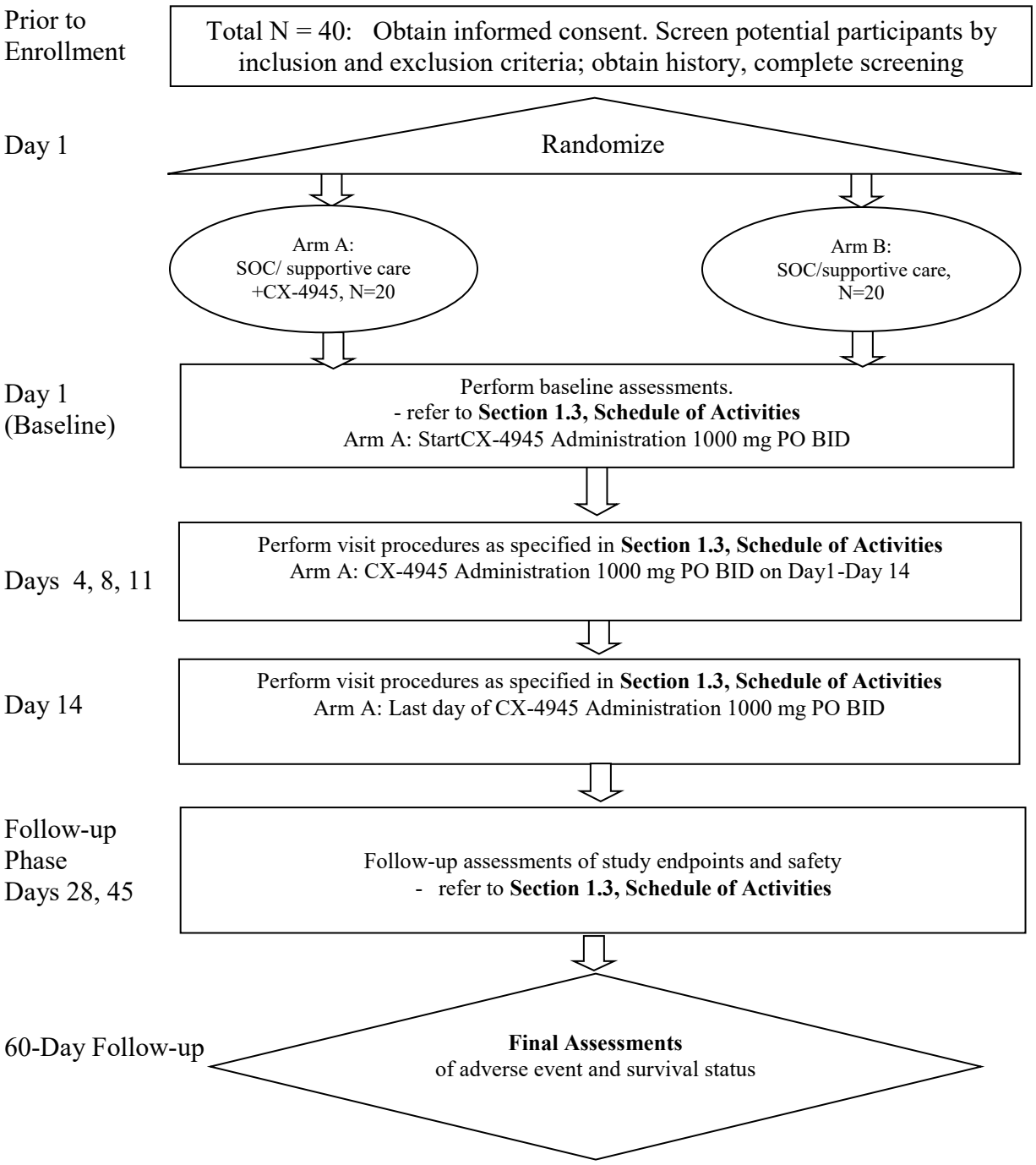
	randomization through Day 28 as compared to the control arm.	2=moderate, and 3=severe). Improvement must be sustained for at least 48 hours. • Number of days from randomization to normalization of fever (defined as <36.6°C from axillary site, or < 37.2°C from oral site or < 37.8°C from rectal or tympanic site), normalization of respiratory rate (< 24 bpm while breathing room air), resolution of hypoxia (defined as SpO2 ≥ 93% in room air or P/F ≥ 300 mmHg). All these improvements must be sustained for at least 48 hours. • Number of days from randomization to the first day on which the subject satisfies one of the following three categories from the ordinal NIAID 8- point Clinical Progression Outcomes scale collected daily from randomization through Day 28: ▪ *Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;* ▪ *Not hospitalized, limitation on activities and/or requiring home oxygen;* ▪ *Not hospitalized, no limitations on activities.*
	To compare changes in clinical status of patients enrolled to CX-4945 treatment arm as compared to the control arm at Day 14 and Day 28.	• Difference in percentage of subjects with clinical recovery compared at Day 14 and Day 28. Clinical recovery is defined as: ▪ Discharge from the hospital, or alleviation of cough (defined as mild or absent in a patient reported scale of 0=absent, 1=mild, 2=moderate, and 3=severe). Improvement must be sustained for at least 48 hours. ▪ normalization of fever (defined as <36.6°C from axillary site, or < 37.2°C from oral site or < 37.8°C from rectal or tympanic site), normalization of respiratory rate (< 24 bpm while breathing room air), resolution of hypoxia (defined as SpO2 ≥ 93% in room air or P/F ≥ 300

		mmHg). All these improvements must be sustained for at least 48 hours. • Percentage of Participants at Each Clinical Status at Day 14 and Day 28 assessed by using the ordinal NIAID 8- point Clinical Progression Outcomes scale: 1) *Death;* *2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);* *3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;* *4) Hospitalized, requiring supplemental oxygen;* *5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);* *6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;* *7) Not hospitalized, limitation on activities and/or requiring home oxygen;* *8) Not hospitalized, no limitations on activities*
	To evaluate preliminary evidence of anti-viral activity of CX-4945 as compared to the control arm.	• Difference in proportions of patients with conversion of positive RT-PCR to negative RT-PCR as assessed at Day 1, Day 8, Day 14 and Day 28. • Changes in chest imaging from Screening to Day 5 or 14 (if applicable) as defined by: o Number of quadrants/ pulmonary lobes affected o Change in number and/or size of COVID-19 pulmonary lesions (ground-glass opacity, consolidation, mix pattern) assessed by chest CT/X-ray

	To evaluate the Clinical Benefit of Silmitasertib (CX-4945) relative to the control arm in patients with Severe COVID-19.	• Days of hospitalization from randomization through Day 28. • Days of supplemental oxygen (if applicable) from randomization through Day 28. • All-cause mortality status - the number of deaths occurred in each treatment group from randomization through Day 60. • Days of non-invasive ventilation/high flow oxygen (if applicable) from randomization through Day 28. • Days of invasive mechanical ventilation/ECMO (if applicable) from randomization through Day 28. • Number of patients returned to room air after randomization through Day 14 or Day 28. • Change in pulse oxygen saturation (SpO2) from randomization to Day 4, 8, 11, 14 and 28. • Number of documented venous thromboembolism (VTE), arterial thrombosis (stroke, myocardial infarction, other) and microthrombosis events from randomization through Day 28. • Changes in EQ-D5-5L (used as an indicator of symptom improvement) from randomization to Day 8, 14 and 28.
	To evaluate changes in inflammatory markers	• Changes in plasma IL-6 level from randomization to Day 4, 8, 11, and 14. • Changes in CRP, LDH, CPK, ferritin, D-dimer from randomization to Day 4, 8, 11, and 14.
Study Population:	This study will enroll male and non-pregnant female patients ≥ 18 years of age with severe Coronavirus Disease 2019 (COVID-19). Approximately 40 patients will be equally randomized in 2 treatment groups.	
Phase:	II	

Description of Sites Enrolling Participants:	All patients will be enrolled at University of Arizona at Banner University Medical Center located in Phoenix or at University of Arizona College of Medicine in Tucson.
Description of Study Intervention:	CX-4945 will be administered twice a day for up to 14 days. The starting dose will be 1000 mg BID (2000 mg total daily dose).
Study Duration:	6 months (from study initiation until completion of data analyses)
Participant Duration:	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.

1.2. SCHEMA


Prior to Enrollment
Total N = 40: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, complete screening
Day 1
Randomize
Arm A: SOC/ supportive care +CX-4945, N=20
Arm B: SOC/supportive care, N=20
Day 1 (Baseline)
Perform baseline assessments.
- refer to Section 1.3, Schedule of Activities
Arm A: StartCX-4945 Administration 1000 mg PO BID
Days 4, 8, 11
Perform visit procedures as specified in Section 1.3, Schedule of Activities
Arm A: CX-4945 Administration 1000 mg PO BID on Day1-Day 14
Day 14
Perform visit procedures as specified in Section 1.3, Schedule of Activities
Arm A: Last day of CX-4945 Administration 1000 mg PO BID
Follow-up Phase Days 28, 45
Follow-up assessments of study endpoints and safety
- refer to Section 1.3, Schedule of Activities
60-Day Follow-up
Final Assessments
of adverse event and survival status

1.3. SCHEDULE OF ACTIVITIES (SOA)

Table 1. Schedule of activities

Procedure/Assessments	**Screening Visit**	**Treatment Phase [16]**					**Follow-Up [17]**		
Day	SV	Day 1 (Baseline)	Day 4	Day 8	Day 11	Day 14	Day 28	Day 45	Day 60
Window Period	Day -7 to Day -1	within 7 days after SV	±1 day	±1 day	±1 day	±1 day	±3 days	±3 days	±3 days
Informed Consent [1]	X								
Eligibility Evaluation [2]	X								
Subject Demographics	X								
Medical History [3]	X								
Physical Examination	X	X[4]		X[4]		X[4]	X[4]	X[4]	
Vital Signs [5]	X	X	X	X	X	X	X	X	
Assessment of clinical recovery [6]		X	X	X	X	X	X	X	
EQ-D5-5L		X		X		X	X		
Clinical Status - Ordinal 8-point Scale Assessment [7]	X	X Daily from Day 1 through Day 28						X	X
Pulse oxygen saturation (SpO2)	X	X	X	X	X	X	X	X	
12-lead ECG	X					X			
Laboratory tests:									
Complete Blood Count [8]	X	X	X	X	X	X	X	X	
Biochemistry [9]	X	X	X	X	X	X	X	X	
Coagulation Indices [10]	X	X	X	X	X	X	X	X	
Serum/Urine Pregnancy Test [11]	X					X			
Urinalysis [12]	X	X	X	X	X	X	X	X	
IL-6 levels		X	X	X	X	X			
PT-PCR[13]	X[13]	X		X		X	X		
Chest radiograph or CT	X	Day 5, Day 14 if indicated [14]							
Randomization [15]		X							
IP Administration (Treatment Arm A only)		Arm A: CX-4945 1000 mg BID PO on Days 1 - 14							

Mortality Status		X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X		
Adverse Events		X	X	X	X	X	X	X	X

[1] Informed consent must be obtained prior to patient participation in any protocol-related activities that are not part of routine care.
[2] Initial evaluation of patient eligibility will be performed by Investigator.
[3] Medical history and current therapies (medications and non-medications).
[4] Symptom-directed physical examination
[5] Vital signs will include blood pressure, heart rate, respiration rate, and temperature.
[6] Based on hospital discharge or normalization of fever, respiratory rate, alleviation of cough, and resolution of hypoxia.
[7] Clinical Assessment to be performed daily for at least 28 days, regardless of discharged or treatment discontinuation. Remote data collection methods, such as electronic data collection, phone, and telehealth assessments can be used from the day of discharge through Day 28, and at every follow-up visit (Days 28, 45 and 60).
[8] Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total and differential count, Absolute Neutrophil Count (ANC) and platelets.
[9] Biochemistry (Comprehensive Metabolic Panel (CMP))

- Hepatic function indicators: total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, lactate dehydrogenase (LDH)
- Renal function indicators: BUN, Serum creatinine, creatinine clearance, or eGFR
- Electrolytes: sodium, potassium, chloride, calcium and bicarbonate
- Other: Creatine phosphokinase (CPK), C-reactive protein (CRP), serum ferritin, d-dimer

[10] Prothrombin time (PT) and International Normalized Ratio (INR)
[11] ONLY performed on women of childbearing potential.
[12] Urine samples will be tested for color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, and microscopic examination of urine sediment.
[13] Positive standard RT-PCR assay or equivalent testing completed within 7 days prior to Day 1 is acceptable for eligibility evaluation at screening.
[14] Chest radiograph or CT will be performed if clinically indicated by the treating physician
[15] **Randomization:** Patient number and treatment arm allocation is performed on Day 1, prior to any Day 1 study assessments
[16] Patient follow-up should continue after discharge via approaches available to the site staff (e.g., telehealth visits, COVID-19 outpatient clinic, telephone calls, texts, and emails to the patient and close contacts).
[17] Follow-up visits may be performed via phone or telehealth, as appropriate

2. INTRODUCTION AND BACKGROUND

2.1. STUDY RATIONALE

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel human pathogen that emerged at the end of 2019 and rapidly spread worldwide caused a global pandemic. SARS-CoV-2, an enveloped, positive-sense, single-stranded RNA beta-coronavirus of the family Coronaviridae that causes COVID-19. 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 and fatigue. Many infected people are asymptomatic or experience mild symptoms and recover without medical intervention. Some patients are more likely to develop a severe respiratory illness including pneumonia, severe acute respiratory syndrome, multi-organ failure, and death.

Along with the development of new antiviral drugs, repurposing of existing drugs for COVID-19 treatment has also accelerated. A number of clinical studies have been conducted to test the efficacy of FDA-approved drugs, re-purposed for COVID-19 (lopinavir, chloroquine, favipiravir, and remdesivir (RDV). At present, the main antiviral strategies currently employed against SARS-CoV-2 can be divided into two types: strategies directly targeting the virus and strategies indirectly targeting the virus via host modulation. Despite some drugs demonstrated good efficacy, there are number of patients not responsive to available anti-COVID-19 therapy. There is no specific antiviral treatment recommended for COVID-19 by Centers for Disease Control and Prevention (CDC). People with COVID-19 should receive supportive care to help relieve symptoms. For severe cases, treatment should include care to support vital organ functions. Clinical management includes symptomatic and supportive care, such as supplemental oxygen, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) when indicated. Therefore, development of an effective antiviral drug for COVID-19 is a global health priority and discovery of novel cellular targets for SARS-Cov2 coronavirus has led to novel putative clinical strategies which merit going into clinical research in COVID-19.

2.2. BACKGROUND

Silmitasertib is a first-in-class small molecule drug that targets Casein Kinase 2 (CK2). Protein kinase CK2 phosphorylates key proteins required to trigger mechanisms vital for viral replication and also is involved in development of host anti-viral immune response. To counter host immune response and create more favorable environment for infection and viral multiplication, viruses have developed an arsenal of strategies. SARS-CoV-2 viral proteins interacting with many human host proteins affect multiple innate immune pathways. One of these key proteins dysregulated by SARS-CoV-2 is the protein kinase CK2. Previous study showed that CK2 is involved in SARS-COV-2 nucleocapsid (N-protein) interactome (virus-host protein interactions). SARS-COV-2 upregulates CK2 to support viral replication, avoid innate immune response and spread virus to nearby cells.

Over activation of CK2 indirectly contribute to successful viral replication and development of cytokine storm.

Researchers noted that the disruption of CK2, promotes the formation of Stress Granules (SGs), resulting in host cell translational arrest and significant limitation of the resources in cells required for viral replication [1]. Besides, SARS-CoV2 uses over activated CK2 in the infected cells to stimulate production of filopodia, as CK2 can promote actin polymerization and regulates cytoskeleton organization. Filopodia with assembled viral particles can invade and transfer the disease in the nearby healthy cells. Induction of virus-containing filopodia are important for SARS-CoV-2 egress and cell-to-cell spread within epithelial monolayers. CK2 is also an important protein for Retinoic acid-inducible gene I (RIG-I) helicase activity regulation. RIG-I is an intracellular RNA virus sensor that mediates a signaling pathway that triggers alpha/beta interferon (IFN-α/β) immune defenses. CK2 phosphorylates a RIG-I repressor domain to inactivate RIG-I in the resting uninfected state. SARs-Cov-2-induced overexpression of CK2 suppresses RIG-I-mediated signaling, while pharmacological inhibition of CK2 enhances expression of IFN-β and suppresses virus proliferation. CK2 signaling appears to be an important pathway hijacked by SARS-CoV-2.

In several pre-clinical and clinical trials in oncology and some other diseases driven by pro-inflammatory cytokines it was demonstrated that CK2 inhibitor CX-4945 significantly reduce cytokine expression (especially IL-6, IL-8, IL-17) and their signaling pathways.

Senhwa's Silmitasertib is a targeted inhibitor of Casein kinase 2 (CK2). Silmitasertib demonstrated strong anti-viral and anti-inflammatory efficacy in vitro in human Calu-3 and HRCE cells and in monkey Vero-6 cell lines infected with SARS-COV-2. As it targets host protein kinase CK2, SARS-COV-2 virus mutations are unlikely to affect Silmitasertib anti-viral or anti-inflammatory efficacy.

Emerging pre-clinical and clinical data and results of independent efficacy evaluation conducted by Utah State University [2], UCSF COVID-19 Research Group [1] and Senhwa Biosciences hypothesize that Silmitasertib (CX-4945) could potentially quell virus-provoked aberrant hyperactivation of the innate immune system by inhibition of upregulated CK2 protein kinase, preferentially restoring normal host cell cytokine regulation, and attenuating viral replication in patients with severe COVID-19, thereby preventing disease progression and improving clinical outcomes. The intended target patient population for treatment with Silmitasertib (CX-4945) are SARS-COV-2 positive patients with severe COVID-19, since in a severe stage of the disease infected cells actively produce viral proteins that dysregulate signaling pathways to allow viruses manipulate host immune responses to create an environment more favorable for infection, that may not be observed in the initial or mild stage of the disease.

CX-4945 demonstrated remarkable clinical benefits under emergency IND authorization in a patient with severe COVID-19 pneumonia not responsive to remdesivir, dexamethasone and

antibiotics and requiring supplemental oxygen. The patient recovered and was discharged from the hospital in five days of treatment with CX-4945.

2.3. SILMITASERTIB (CX-4945)

Silmitasertib (CX-4945) is a first-in-class potent and highly selective small molecule inhibitor of CK2 that interacts competitively with the ATP-binding site of CK2 subunit alpha, leading towards the inhibition of several downstream signaling pathways. CK2 is involved in regulation of signaling pathways (Sonic Hedgehog (SHH), IL-6/STAT3, mTOR signaling pathways) through protein phosphorylation and also plays a multifunctional role in signal transduction, transcriptional control, apoptosis and inflammation. Overexpression of CK2 was observed in diseases with high proliferative activities, inflammatory reaction and dysregulated immune response (viral infections, auto-immune inflammations, cancer).

The biological activity of CX-4945 has been evaluated in both in vitro and in vivo studies:

- CX-4945 demonstrated strong anti-viral efficacy in human cells infected by SARS-CoV-2 (pre-clinical in vitro study). [2] (https://www.biorxiv.org/content/10.1101/2020.04.21.054387v1)
- CX-4945 significantly reduced replication of human papillomavirus in vivo. [3]
- In several pre-clinical and clinical trials in the diseases driven by pro-inflammatory cytokines CX-4945 demonstrated anability to significantly reduce plasma level of interleukins (IL-6, IL-8, IL-17) in vitro and in vivo (inflammatory breast cancer, Alzheimer's disease, autoimmune encephalomyelitis). [4]
- CK2 inhibitor down-regulated replication, budding and release of influenza virus in pre-clinical studies. [5]
- CK2 inhibitor reduced phosphorylation dependent ICP27 protein export, which is necessary for its ability to export herpes simplex viral RNAs. [6]
- CX-4945 also demonstrated anti-tumor activity in a variety of primary human xenografts and tumor cell line xenograft models and in clinical trials.

Silmitasertib (CX-4945) is currently under development in several oncology programs in adults and in children with recurrent/advanced or metastatic cancer. CX-4945 is being used as an antitumor agent that inhibits the Sonic Hedgehog signaling pathway (basal cell carcinoma, medulloblastoma) and/or DNA repair in tumor cells damaged by chemotherapy (cholangiocarcinoma) through inhibition of CK2. Three phase I clinical trials of CX-4945 in cancer patients have been completed to date (solid tumors, multiple myeloma), and there is one ongoing phase I study (BCC) and two ongoing phase II studies (CCA, Medulloblastoma).

Approximately 200 patients have been treated with CX-4945 to date.

All patients in the completed trials had advanced and/or relapsed or refractory cancer and had undergone previous cancer treatments. The median age of the patients was ≥60 years, and all were taking concomitant medications during the studies.

CX-4945 was generally well-tolerated when administered following a twice-daily (bid) or four times-daily (QID) oral dosing schedule for 21 days followed by 7 days of rest. Most adverse events reported were mild to moderate in severity. The most common toxicities associated with CX-4945 were gastrointestinal disorders, including diarrhea, nausea and vomiting. Other frequently reported drug-related adverse events were hypokalemia and fatigue. Severe adverse events related to CX-4945 were diarrhea, hypokalemia, hyponatremia, hypophosphatemia and lymphopenia.

Most toxicities related to CX-4945 were manageable with drug discontinuation, use of antidiarrheal medication and potassium supplementation.

The highest planned dose, 1000 mg bid, was found to be safe and tolerable. At this dose, 1 out of 12 patients experienced DLT, grade 4 hypokalemia.

Generally, dose dependent peak plasma concentrations and AUC have been observed in the pharmacokinetic studies at steady state during both the twice daily and four-times daily administration of CX-4945. The observed terminal half-life at steady state is approximately 15 hours.

Dose-proportional (Cmax and AUC) biomarker effects have been observed in CX-4945-treated patients, including reduced phosphorylation of Akt and p21 in PBMCs beginning with the 300 mg bid dose level and 300 mg QID dose level. Reduced levels of plasma IL-6 and IL-8 have also been observed.

The existing safety and pharmacokinetic data generated from prior studies, supports the planned dosing frequency of twice daily (BID) for up to 14 days under the expanded access use for the severe COVID-19 indication.

CX-4945 was used in a patient with severe COVID-19 pneumonia under emergency IND authorization. The patient had been treated with multiple therapeutics within two weeks, but remained hypoxic and required up to 2 liters of supplemental oxygen daily. Within 24 hours of the first dose of CX-4945 the oxygen requirement was weaned to room air. No drug-related toxicities were observed. The patient was discharged from the hospital within five days.

The purpose of this open-label, 2 arm parallel-group, randomized, controlled interventional prospective exploratory, Investigator-Initiated Trial (IIT) in 40 patients is to evaluate safety and tolerability of Silmitasertib (CX-4945) 1000 mg BID dose. Secondary objectives will be used to make an initial assessment of the potential for clinical benefit. The drug supplier, Senhwa

Biosciences, is taking steps toward a subsequent randomized, double-blind, placebo-controlled study in a large number of subjects (NIH-sponsored ACTIV study).

2.4. RISK/BENEFIT ASSESSMENT

Silmitasertib is a generally well-tolerated medication. Most adverse events reported were mild to moderate in severity. The most common toxicities associated with CX-4945 were gastrointestinal disorders, manageable with drug discontinuation or use of anti-diarrheal medication. Based on the currently available data, the identified or potential risks of the product do not outweigh its identified or potential benefits.

3. OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoint
• To assess safety and tolerability of CX-4945 administered orally twice daily to patients with severe COVID-19	• Adverse Events experienced by patients from randomization to Day 60 (including vital signs, physical findings, clinical laboratory, and ECG results) as characterized by type, frequency, severity (as graded by Common Terminology Criteria for Adverse Events (CTCAE version 5.0), timing, seriousness, and relationship to study therapy.
Secondary Objectives	**Secondary Endpoints**
• To compare time to clinical recovery in the CX-4945 treatment group evaluated from randomization through Day 28 as compared to the control arm.	• Number of days from randomization to discharge, or alleviation of cough (defined as mild or absent in a patient reported scale of 0=absent, 1=mild, 2=moderate, and 3=severe). Improvement must be sustained for at least 48 hours. • Number of days from randomization to normalization of fever (defined as <36.6°C from axillary site, or < 37.2°C from oral site or < 37.8°C from rectal or tympanic site), normalization of respiratory rate (< 24 bpm while breathing room air), resolution of hypoxia (defined as SpO2 ≥ 93% in room air or P/F ≥ 300 mmHg). All these improvements must be sustained for at least 48 hours. • Number of days from randomization to the first day on which the subject satisfies one of the following three categories from the ordinal NIAID 8-point Clinical Progression Outcomes scale collected daily from randomization through Day 28: o *Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;* o *Not hospitalized, limitation on activities and/or requiring home oxygen;* o *Not hospitalized, no limitations on activities.*
• To compare changes in clinical status of patients enrolled to CX-4945 treatment arm as	• Difference in percentage of subjects with clinical recovery compared at Day 14 and Day 28. Clinical recovery is defined as:

compared to the control arm at Day 14 and Day 28.	▪ Discharge from the hospital, or alleviation of cough (defined as mild or absent in a patient reported scale of 0=absent, 1=mild, 2=moderate, and 3=severe). Improvement must be sustained for at least 48 hours. ▪ normalization of fever (defined as <36.6°C from axillary site, or < 37.2°C from oral site or < 37.8°C from rectal or tympanic site), normalization of respiratory rate (< 24 bpm while breathing room air), resolution of hypoxia (defined as SpO2 ≥ 93% in room air or P/F ≥ 300 mmHg). All these improvements must be sustained for at least 48 hours. • Percentage of participants at each clinical status at Day 14 and Day 28 assessed by using the ordinal NIAID 8- point Clinical Progression Outcomes scale: 1) *Death;* *2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);* *3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;* *4) Hospitalized, requiring supplemental oxygen;* *5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);* *6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;* *7) Not hospitalized, limitation on activities and/or requiring home oxygen;* *8) Not hospitalized, no limitations on activities*
• To evaluate preliminary evidence of anti-viral activity of CX-4945 as compared to the control arm.	• Difference in proportions of patients with conversion of positive RT-PCR to negative RT-PCR as assessed at Day 1, Day 8, Day 14 and Day 28.. • Changes in chest imaging from Screening (Day 0)to Day 5 or Day 14 (if applicable) as defined by: o Number of quadrants/ pulmonary lobes affected

	○ Change in number and/or size of COVID-19 pulmonary lesions (ground-glass opacity, consolidation, mix pattern) assessed by chest CT/X-ray
• To evaluate the Clinical Benefit of Silmitasertib (CX-4945) relative to the control arm in patients with Severe COVID-19.	• Days of hospitalization from randomization through Day 28. • Days of supplemental oxygen (if applicable) from randomization through Day 28. • All-cause mortality status: the number of deaths occurred in each treatment group from randomization through Day 60. • Days of non-invasive ventilation/high flow oxygen (if applicable) from randomization through Day 28. • Days of invasive mechanical ventilation/ECMO (if applicable) from randomization through Day 28. • Number of patients returned to room air after randomization through Day 14 or Day 28. • Change in pulse oxygen saturation (SpO2) from randomization to Day 4, 8, 11, 14 and 28. • Number of documented venous thromboembolism (VTE), arterial thrombosis (stroke, myocardial infarction, other) and microthrombosis events from randomization through Day 28. • Changes in EQ-D5-5L (used as an indicator of symptom improvement) from randomization to Day 8, 14 and 28.
• To evaluate changes in inflammatory markers	• Changes in plasma IL-6 level from randomization to Day 4, 8, 11, and 14 • Changes in CRP, LDH, CPK, ferritin, D-dimer from randomization to Day 4, 8, 11, and 14

4. STUDY DESIGN

4.1. OVERALL DESIGN

This is a phase II multi-center, randomized, open-label, 2 arm parallel-group controlled interventional prospective study of CX-4945 in patients with severe COVID-19. Up to approximately 40 patients will be enrolled into this study. A screening evaluation will occur within 7 days prior to Day 1. All qualified patients will be randomized at Day 1 in a ratio of 1:1 to one of the following two treatment arms:

- **Arm A:** SOC*/ best supportive care** in combination with CX-4945 1000 mg BID PO or
- **Arm B:** SOC*/ best supportive care** alone

** The standard of care (SOC) is not pre-specified, may vary among patients, and may include agents with anti-viral activity, such as remdesivir, among others. Investigator discretion is to be applied for any established SOC. Active concomitant treatment with other investigational antivirals or immunomodulators are not permitted*

*** Best supportive care is defined as intensive care therapy according to current guidelines, evidence, and best practice, including but not limited to lung protective ventilation, thrombosis prophylaxis, renal replacement therapy when indicated, and access to advanced therapies including extracorporeal membrane oxygenation.*

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 the screening) will be up to 67 days. For details on randomization see Randomization in **Section 6.1.2.**

4.2. JUSTIFICATION FOR DOSE

CX-4945 will be administered twice a day for up to 14 days. The starting dose will be 1000 mg BID (2000 mg total daily dose). This starting dose is based on three completed Phase I studies where patients were administered CX-4945 following a twice-daily (BID) or four-times-daily (QID) dosing regimen for 21 days followed by 7 days of rest. A total of 12 patients were treated in single agent studies at the 1000 mg bid dose level. Additionally, the safety and tolerability of 28 day continuous dosing of CX-4945 at 1000 mg BID was verified during an ongoing Basal Cell Carcinoma (BCC) study with 12 subjects enrolled to date. In total, approximately 115 patients have been treated with 1000 mg twice daily dosing of CX-4945 in several completed and ongoing studies.

4.3. END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the treatment phase and follow-up visits at Day 28, Day 45, and Day 60.

Discontinuation from the study drug does not mean the withdrawal from the study assessments. Subjects who discontinued therapy should remain in the study and continue follow-up for key outcomes. The only reasons for study withdrawal are withdrawal of consent and loss to follow-up.

5. STUDY POPULATION

This study will enroll up to approximately 40 patients with severe Coronavirus Disease 2019 (COVID-19). All study participants will be identified from the currently hospitalized patients. SOC/Best supportive care alone or in combination with CX-4945 will be given to study subjects.

5.1. PATIENT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

5.1.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Male or non-pregnant female adult ≥ 18 years of age
2. Diagnosed or confirmation of COVID-19 infection by standard RT-PCR assay or equivalent testing within 7 days prior to randomization (Day1).
3. Hospitalized patient with severe illness caused by SARS-CoV-2 (**Note:** Prior or current use of remdesivir or dexamethasone (SOC) are allowed under the investigator's discretion. Concomitant treatment with other investigational antiviral drugs or immunomodulators are not permitted from Day1 through Day 28)

    - Symptoms of severe systemic illness/infection with COVID-19:
        - At least 1 of the following: fever, cough, sore throat, malaise, headache, muscle pain, shortness of breath at rest or with exertion, confusion, or symptoms of severe lower respiratory infection including dyspnea at rest or respiratory distress

    AND

    - Clinical signs indicative of severe systemic illness/infection with COVID-19
        - At least 1 of the following: RR ≥ 30, HR ≥ 125, SaO2 <93% on room air or requires ≥ 2L oxygen in order to normalize SaO2.
4. Patient (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
5. Adequate hematopoietic capacity, as defined by the following:
    a. Hemoglobin ≥ 9.0 g/dL and not transfusion dependent
    b. Platelets ≥ 100,000/mm^3
    c. Absolute neutrophil count ≥ 1500 cells/mm^3

6. Adequate hepatic function, as defined by the following:
    a. AST and ALT ≤ 2.5 times upper limit of normal (ULN)
    b. Total bilirubin ≤ 1.5 x ULN
    c. Albumin ≥ 2.5 g/dL
7. Absence of any active or recurring clinically significant hepatic disease and adequate renal function, as defined by the following:
    a. Renal: calculated creatinine clearance >45 mL/min for patients with abnormal, increased creatinine levels (Cockcroft-Gault formula).
8. Ability to take oral medication and be willing to adhere to drug administration and premedication requirements (see **Section 6.3**) throughout study duration.

5.1.2. Exclusion Criteria

Potential subjects meeting any of the following criteria will be excluded from participation in this study:

1. Patient showing signs of respiratory failure necessitating mechanical ventilation
2. Pregnant or nursing women.

    NOTE: Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; or abstinence) prior to study entry and for the duration of study participation. Should a man father a child, or a woman become pregnant or suspect she is pregnant while participating in this study, he or she should inform the treating physician immediately.
3. Active or uncontrolled infections other than COVID-19 or with serious illnesses or medical conditions which would not permit the patient to receive study treatment
4. Active or planned concomitant treatment with other investigational antivirals or immunomodulators
5. Chronic diarrhea (excess of 2-3 stools/day above normal frequency)
6. Current use or anticipated need for drugs that are known strong inhibitors or inducers of major CYP enzymes.

5.2. SCREEN FAILURES

All subjects who fail to meet eligibility criteria are considered screen failures, and are exited from the study. Subject number, demographics and reason for screen failure will be recorded.

If a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject will be re-consented and assigned a new unique identification number at the time of re-screening and may be enrolled if they are found to meet all inclusion and no exclusion criteria at the subsequent screening visit.

6. STUDY TREATMENT

6.1. STUDY TREATMENT ADMINISTRATION

6.1.1. Investigational Drug Product Description

For this study, the investigational product is CX-4945 that will be assigned to the subjects randomized to the treatment Arm A.

Refer to Investigator Brochure or summary of product characteristics.

All subjects enrolled in the study (Arm A and Arm B) may be treated with SOC/best supportive care as per the investigator's discretion and in accordance with the site standard clinical practice. The patients randomized to the treatment Arm A will receive SOC/best supportive care therapy in combination with CX-4945. The patients randomized to the control Arm B will receive SOC/best supportive care alone.

6.1.2. Randomization

Randomized treatment assignments for the subjects will be done after confirmation of subject's eligibility, and prior to any other Day 1 study assessments. Subjects will be allocated randomly into Arm A and Arm B in a 1:1 ratio.

Table 2. Method of Assignment to Treatment

Arm	SOC/ SUPPORTIVE CARE	Daily dose of CX-4945 (mg)	Dose administration b.i.d. (mg)	AM Dose (mg)	PM Dose (mg)	No. of capsules/day
A	Assigned by the investigator	2000	1000	1000	1000	10
B	Assigned by the investigator	0	0	0	0	0

*****SOC and Supportive Care are defined in Section 4.1.

6.1.3. Dosing and Administration of CX-4945

Patients enrolled to the treatment Arm A will receive 1000 mg of CX-4945 twice daily by mouth, beginning on Day 1, and continuously through Day 14.

Patients will be instructed to take oral antiemetic prophylaxis at least 1 hour prior to taking the study drug. Other oral medications should be taken at least one hour before or 2 hours after ingesting the dose of CX-4945 capsules.

Patients will take five 200-mg CX-4945 capsules twice daily, two hours after the morning meal and two hours after the evening meal (dinner) with water. Patients are advised to take 1 capsule at a time with a pause in between each. This method may prevent a clumping effected in the stomach, so patient can take as much as 10 minutes to swallow each capsule.

The study drug will be taken on an empty stomach with at least six ounces (180 mL) of water. After CX-4945 administration, the patient will be NPO (except for water) for 2 hours, after which, the patient may eat.

6.1.4. Investigational Product Compliance

Site staff will dispense Investigational Product (CX-4945) to the study subjects randomized to the Treatment Arm A. If a patient misses a dose, he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up and should be documented in the dosing record form. Patients will be instructed to return any unused capsules. The number of tablets/capsules returned by the patient will be counted, documented, and recorded.

6.1.5. Silmitasertib (CX-4945) Dose Modifications

The most common drug related adverse events reported for CX-4945 are predominantly gastrointestinal disorders, including nausea, vomiting and diarrhea. The dose interruption, reduction, and permanent discontinuation for any toxicity are described below. Dose modification instructions provided bellow do not substitute for investigators' medical judgement. Investigators should always manage their patients according to their medical judgement based on the particular clinical circumstances.

Table 3. Silmitasertib (CX-4945) Dose Modification and Management for potential toxicities (attributable to Silmitasertib)

CTCAE 5.0 Grade (attributable to Silmitasertib)	Treatment Modifications
Grade 1	Treat on time. dose reduction is not required
Grade 2	Hold until≤ Grade 1, resume at same dose
Grade 3	Hold until< Grade 2, resume at dose reduced by 1 level (200 mg)
Grade 4	Hold until< Grade 2, resume at dose reduced by 1 level (200 mg). Permanent discontinuation can be considered by at the Investigator's discretion

- **Dose Reduction:** If a dose-response relationship for toxicity is observed, a reduced dose can be given to the subject. Dose adjustments will be allowed based on the toxicity, efficacy evaluation, and clinical judgment by physician.

- **Dose Interruption:** Refer to Table 3 above. Recovery to acceptable levels must occur to allow Silmitasertib (CX-4945) continuation.
- **Dose Discontinuation:** Treatment with CX-4945 can be discontinued prematurely due to the following reasons:
    - Disease Progression
    - Respiratory failure requiring invasive mechanical ventilation,
        - Shock (defined by SBP < 90 mm Hg, or Diastolic BP < 60 mm Hg), or
        - Multiple organ dysfunction/failure
        - Intolerable toxicity most probably attributable to CX-4945.
    - Pregnancy
    - Significant study therapy non-compliance
    - If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued treatment under the protocol would not be in the best interest of the participant
    - Withdrawal of consent from study treatment or participation

  Discontinuation from the study drug does not mean the withdrawal from the study assessments. Subjects who discontinued therapy should remain in the study and continue follow-up for key outcomes. The only reasons for study withdrawal are withdrawal of consent from study participation and loss to follow-up.

6.2. INVESTIGATIONAL PRODUCT SUPPLIES, STORAGE AND ACCOUNTABILITY

6.2.1. Investigational Product Supplies

CX-4945 will be supplied by Senhwa Biosciences. Study center will receive CX-4945 prior to enrollment of the first patient. The clinical site pharmacy /qualified staff member will dispense the supplies to the patients enrolled to the treatment Arm A in quantities appropriate for the study visit schedule. Any unused product or waste material should be disposed of in accordance with local requirements.

6.2.2. Formulation, Appearance and Packaging

CX-4945-PIC has been manufactured as neat API powder in hard shell gelatin capsules (Capsugel) in a dose strength of 200 mg capsules (Powder in Capsule (PIC) formulation), for immediate release, oral administration. There are no excipients used for PIC formulation.

Clinical trial material supply of CX-4945-PIC for oral administration are supplied as 200 mg strength in size 1, opaque blue capsules, contained in 60 cc, wide mouth, white, high-density

polyethylene (HDPE) bottles. Each bottle contains fifteen capsules with one (1 gram), white plastic PTC-0005 desiccant pod, and is induction heat sealed.

6.2.3. Product Storage and Stability

CX-4945 clinical trial material should be stored in the container provided, between 15°C-30°C (59°F-86°F), and should be protected from moisture, freezing, and bright light.

6.3. CONCOMITANT MEDICATION

6.3.1. Premedication - Antiemetic Drugs (Mandatory)

All patients assigned to treatment with CX-4945 (Arm A) will take an oral 5-HT3 antagonist daily, at least 1 hour prior to taking the CX-4945 capsules or a 5-HT3 antagonist transdermal patch at least 24 hours prior to taking the CX-4945 capsules every 7 days. If a patient prefers 5-HT3 antagonist transdermal patch, the patient is expected to apply the patch approximately 24 hours before the day 1. If the patch is missed, the patient will be suggested to taking the oral 5-HT3 antagonist 1 hour before taking CX-4945 on day 1 and continue taking the oral 5-HT3 antagonist for 7 days in order to switch to an antagonist patch.

Medications within the 5-HT3 antagonist class are interchangeable depending on availability and tolerability. Dose(s) of the antiemetic medication, either intensity or frequency can be adjusted as clinically indicated. Patients should receive enough supply to cover the entire treatment.

5-HT_3 antagonist (choose one)
- Dolasetron 100 mg PO daily - Granisetron 1 mg PO twice daily; the first 1 mg dose should be given up to 1 hour before CX-4945 (with second 1 mg dose 12 hours later) or 3.1 mg/24-h transdermal patch every 7 days - Ondansetron 8 mg PO twice daily; the first 8 mg dose should be given up to 1 hour before CX-4945 (repeat dose 8 hours after the initial dose)

Management of breakthrough nausea and vomiting should take place as necessary.

6.3.2. Anti-Diarrheal Medication (Recommended):

- All patients assigned to treatment with CX-4945 (Arm A) should be advised to obtain an adequate supply of loperamide (IMODIUM®) with explicit instructions for the management of diarrhea.
- Early diarrhea or abdominal cramps occurring within the first 24 hours is treated with atropine 0.3 - 1.2 mg IV or SC. Prophylactic atropine may be required for subsequent treatments.

- Late diarrhea has a median onset of 2 days post-treatment with CX-4945 and must be treated with loperamide (e.g., IMODIUM®). Instruct patient to have loperamide on hand and start treatment at the first poorly formed or loose stool, or earliest onset of more frequent stool than usual:
    - 4 mg start
    - then 2 mg every 2 hours until diarrhea-free for 12 hours
    - may take 4 mg every 4 hours at night

6.3.3. Electrolyte Abnormalities

Electrolyte abnormalities are common adverse events with Silmitasertib (CX-4945) which may predispose subjects to arrythmias.

a. Mandatory 5-HT3 antagonist pre-medication may compound this effect. To adequately monitor for this risk, a 24-hour telemetry monitoring for subjects with electrolyte abnormalities may be performed, if clinically indicated.
b. Use of atropine as an anti-diarrheal medication may also compound this effect. Investigator should consider use of another anti-diarrheal agent for subjects who have persistent diarrhea despite use of loperamide.

6.4. SILMITASERTIB (CX-4945) DRUG INTERACTION

6.4.1. Effect of CX-4945 in Human Liver Microsomes

The absorption, distribution, metabolism, and excretion (ADME) properties of CX-4945 have been evaluated in in vivo to support nonclinical safety evaluations and to assess the potential relevance to humans. CX-4945 was tested in a non-GLP in vitro ADME-TOX in human liver microsomes with the following seven key CYP450 isoenzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. CX-4945 did not show significant inhibition or induction of any CYP isoenzymes tested in this study (for all isozymes more than 80 percent remained after 60 minutes and it was not possible to calculate a specific half-life).

The result suggests that CX 4945 does not inhibit or induce these seven CYP450 isozymes, and can therefore be safely co-administered with drugs that are metabolized via this pathway.

Antiemetic drugs (5-HT3 antagonist) are required and anti-diarrheal drugs are recommended for concomitant use in the treatment group A for management of possible GI toxicities. CYP3A4 is the predominant enzyme pathway for ondandestron and granisteron metabolism. Loperamide is metabolized by the cytochrome P450 (CYP) system and is a substrate for the CYP3A4 isoenzyme. Approximately 200 subjects have been treated with CX-4945 in Phase I/II clinical trials to date and approximately 115 subjects received required and /or recommended concomitant treatment with

antiemetic and antidiarrheal drugs. CX-4945 was safely co-administered with concomitant medications with no drug-drug interaction (DDI) observed.

Because complete CX-4945 metabolism information is not available at this point and treatment with 5-HT3 antagonist and anti-diarrheal drugs is planned for treatment arm A, current use or anticipated need for drugs that are known strong inhibitors or inducers of major CYP enzymes should be avoided from Day 1 through Day 14. If the replacement is not possible, then patients taking strong inhibitors or inducers of major CYP enzymes should not be enrolled to the study (exclusion criterion #6).

7. STUDY DISCONTINUATION

7.1. SUBJECT COMPLETION

A participant is considered to have completed the study if he or she has completed the treatment phase and follow-up visits at Day 28, Day 45, and Day 60. Documentation to whether or not each subject completed the clinical study will be recorded.

7.2. SUBJECT WITHDRAWAL FROM PARTICIPATION

At any point during the study and without prejudice to future care, all subjects have the right to withdraw from participation, refusing to complete scheduled study assessments and follow-ups. The reason for withdrawal from participation will be recorded in the subject medical records.

All patients who discontinued therapy but maintain consent for study participation to be followed for outcome information and should remain in the study through the end of assessment and follow-up period for all important safety and anti-viral activity data collection and evaluation. The only reasons for withdrawal from participation should be withdrawal of consent and loss to follow-up. Before a subject is identified as lost-to-follow up, the site should make all reasonable efforts to contact the subject. These attempts must be documented and should include at a minimum one phone call and one certified letter.

7.3. SUBJECT DISCONTINUATION FROM STUDY TREATMENT

The Investigator can discontinue a subject from study therapy at any time if in his clinical judgment considers to be medically necessary. Investigators considering discontinuing study treatment should contact the medical monitor prior to such discontinuation. The reason(s) for discontinuation of study treatment should be documented in sourse records. Subjects who have study treatment discontinued will continue to be followed, per protocol, whenever possible. If visits to the site are not possible after discharge, subjects can be followed via telehealth or other approaches (telephone calls, e-mails, and texts) to ascertain vital status in all subjects.
Subjects who have study treatment discontinued due to a serious adverse event will be followed until resolution or stabilization of the event.
Discontinuation from the study therapy does not mean the withdrawal from participation. Every attempt should be made to collect follow-up information to minimize missing data in this study.

An investigator may discontinue a participant from the study therapy for the following reasons:

- Pregnancy
- Significant study therapy non-compliance
- If any clinical adverse event (AE) or serious adverse event (SAE), laboratory abnormality, or other medical condition or situation occurs such that continued treatment under the protocol would not be in the best interest of the participant

- Disease progression which requires discontinuation of the study therapy
- Significant study therapy non-compliance
- Withdrawal of consent from study treatment

In the event that a subject is withdrawn from the study treatment at any time due to an adverse event or SAE, the procedures stated in Section 8.3 (Safety) must be followed.

8. STUDY ASSESSMENTS AND PROCEDURES

The study will have three phases: Screening Phase/Visit, Treatment Phase, and Follow-Up Phase. A schedule of assessments and procedures is provided in **Section 1.3.**

Due to risk of infection for study staff and hospital personnel, the site may take steps to limit face-to-face interaction (i.e. telehealth or eSignature).

8.1. STUDY PROCEDURES

8.1.1. Screening Period:

The subject will sign and date the informed consent form (ICF) and Health Insurance Portability Accountability Act (HIPAA) authorization (according to site policy and practices) prior to any study-related procedures. The study center will maintain the study-specific screening and enrollment logs at their site.

For screening procedures see the Schedule of Activities in **Section 1.3** and Assessments in **Section 8.2**.

8.1.2. Treatment Period:

For the treatment period procedures see the Schedule of Activities in **Section 1.3** and Assessments in **Section 8.2**.

Subjects who meet the eligibility criteria will be randomized prior to any other Day 1 study procedures. The following evaluations and assessments should be performed on Day 1prior to treatment: review of any changes in medication history, physical examination, vital signs, clinical status – ordinal scale assessment, EQ-D5-5L questionnaire, pulse oxygen saturation (SpO2), PT-PCR, laboratory sample collection for routine serum biochemical, hematologic, coagulation, and IL6 levels analysis.

Patient follow-up should continue after discharge via approaches available to the site staff (e.g., telehealth visits, COVID-19 outpatient clinic, telephone calls, texts, and emails to the patient and close contacts). These efforts should prevent missing data while limiting additional public health risks and unnecessary community exposure.

During the treatment phase, subjects randomized to the treatment arm A will receive CX-4945 (1000 mg) twice a day for up to 14 days. Details on study drug administration can be found in **Section 6**.

8.1.3. Follow Up Period

For follow-up procedures see the Schedule of Activities in **Section 1.3** and Assessments in **Section 8.2**.

8.1.4. Unscheduled Visits

In the event that the subject will return to clinic at a time other than a regularly scheduled study visit, the visit will be regarded as an unscheduled visit. Assessments at unscheduled visits are at the discretion of the Investigator. All pertinent findings, including adverse events or changes in medications, will be noted in the subject medical records.

8.2. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

8.2.1. Safety Assessment

Safety assessments will include collection of AEs, serious adverse events (SAEs), vital signs and physical examination, electrocardiogram (ECG [12-lead]), laboratory assessments, including pregnancy tests and verification of concomitant treatments.

8.2.1.1. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. For female patients of childbearing potential, a negative pregnancy test is required before receiving CX-4945 (1 negative pregnancy test at screening). Following a negative pregnancy test result at screening, appropriate contraception must be commenced: the study candidate should have used 2 forms of contraception. Pregnancy tests will also be repeated at Day 14 to confirm that the patient has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the study and when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product but may remain in the study.

8.2.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the CTCAE version 5.0) timing, seriousness, and relatedness. For AE assessment details, see **Section 8.3.3**. Investigator will follow-up for any AEs/SAEs and mortality status at Day 28, Day 45 and Day 60.

8.2.1.3. Vital Signs and Physical Examination

Patients will have a full physical examination to include an examination of all major body systems, height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider, as acceptable according to local regulation. A symptom-directed physical examination should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, and systems associated with symptoms). Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as an adverse event.

Pulse oximetry should be collected prior to collection of the blood pressure, pulse rate, and temperature. Oxygen levels should be evaluated on the finger in accordance with the site standard procedures. All abnormalities will be evaluated by the study physician.

Blood pressure, heart rate, respiration rate, and temperature should be recorded after approximately 5 minutes rest. An abbreviated physical exam is an assessment for emergent toxicities or changes from prior visits and a symptom directed exam conducted by a physician, trained physician's assistant or nurse practitioner, as acceptable according to local regulation.

8.2.1.4. Laboratory Safety Assessment

Hematology and blood chemistry will be drawn at the time points described in the Schedule of Activities (see **Section 1.3**) and analyzed at local laboratories. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns. Samples for hematology, blood chemistry, coagulation, pregnancy and urinalysis will be analyzed by the site's local laboratory.

Table 4. Safety Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis	Pregnancy Test
Hemoglobin	ALT	PT or INR	color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen	For female patients of childbearing potential, serum or urine
Hematocrit	AST			
RBC	Alk Phos			
Platelets	LDH			
WBC	Total Protein			
Absolute Neutrophils	Sodium			

Hematology	Chemistry	Coagulation	Urinalysis	Pregnancy Test
Absolute Lymphocytes	Potassium		microscopic examination of urine sediment	
Absolute Monocytes	Ferritin			
Absolute Eosinophils	Chloride			
Absolute Basophils	Calcium			
	Bicarbonate			
	Total bilirubin			
	d-dimer			
	Creatine (serum)			
	BUN			
	Albumin			
	C-reactive Protein (CRP)			
	Creatinine Clearance			
	IL-6			
	Creatine Phosphokinase (CPK)			
	eGFR			

8.2.1.5. **Electrocardiogram**

Electrocardiogram (ECG): ECG will be done at Screening and at Day 14. It is preferable that the machine used has a capacity to calculate the standard intervals automatically, including QT and QTc interval. At each time point (see the Schedule of Activities), if the significant abnormalities (>Grade 2) in ECG intervals are revealed, then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate.

8.2.1.6. **Other Assessments**

To adequately monitor for the risk of 5-HT3 antagonist pre-medication which may predispose subjects to arrythmias, a 24-hour telemetry monitoring for subjects with electrolyte abnormalities may be performed, if clinically indicated.

8.2.2. **Efficacy/Anti-viral Activity Assessment**

8.2.2.1. **Clinical Evaluation to Assess Recovery**

Assessment of recovery at the time points described in the Schedule of Activities (see **Section 1.3**) is based on hospital discharge or normalization of fever, respiratory rate, alleviation of cough, and resolution of hypoxia. Normalization of fever (defined as <36.6°C from axillary site, or < 37.2°C from oral site or < 37.8°C from rectal or tympanic site), respiratory rate (< 24 bpm while breathing room air), alleviation of cough (defined as mild or absent in a patient reported scale of 0=absent, 1=mild, 2=moderate, and 3=severe) and resolution of hypoxia (defined as SpO2 ≥ 93% in room air or P/F ≥ 300 mmHg) must be sustained for at least 48 hours.

8.2.2.2. **EQ-D5-5L**

Administration of questionnaires for patient-reported outcomes at the time points described in the Schedule of Activities. The 5-level EQ-5D version (EQ-5D-5L) will be used to assess five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

8.2.2.3. **COVID-19 8-Point Clinical Progression Outcomes Scale**

Progression is assessed on COVID-19 8-point ordinal scale collected daily from randomization through Day 28, regardless of discharge or treatment discontinuation status, to adequately capture relevant COVID19 outcomes. Remote data collection methods, such as electronic data collection, phone, and telehealth assessments can be used after patient discharge from the hospital through Day 28 (see **Section 1.3**). The ordinal scale of patient health status ranges from: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities.

8.2.2.4. **Pulse Oxygen Saturation (SpO2):**

Measuring the amount of oxygen-carrying hemoglobin in the blood relative to the amount of hemoglobin not carrying oxygen will be done at the time points described in the Schedule of Activities (see **Section 1.3**).

8.2.2.5. **Laboratory Assessment of Changes and Trend in Inflammatory Markers**

Laboratory tests for IL-6 CRP, LDH, CPK, ferritin and D-dimer levels will be done at the time points described in the Schedule of Activities (see **Section 1.3**) to evaluate early markers of inflammation response. Laboratory tests will be performed locally, at CLIA certified local laboratory following the site's best practices.

- Ferritin levels may be useful early markers of disease progression or dysregulated immune response.
- D-dimer level is associated with pro-inflammatory cytokine cascade and development of cytokine storm.
- CRP produced by the liver in response to IL-6 is a marker of inflammation and rapid increase of CRP level is a marker of increased risk of cytokine storm development.

8.2.2.6. **RT-PCR**

RT-PCR will be done at the time points described in the Schedule of Activities (see **Section 1.3**). At screening positive RT-PCR result (presence of SARS-COV-2 RNA) is required for inclusion criterion evaluation. Local, fully validated, RT-PCR tests shall be performed in a CLIA-certified and CAP-accredited laboratory.

8.2.2.7. **Chest Radiograph or CT**

Chest X-ray or chest CT will be done and evaluated locally according to the standard site practice at the time points described in the Schedule of Activities (see **Section 1.3**). Responses to CX-4945 administration will be followed on radiograph or CT scans using the Response Evaluation in COVID-19 patients with pneumonia. The chest-CT analysis will be performed considering number of pulmonary lesions, lesion's extend, number of pulmonary lobes affected, and common COVID-19 typical abnormalities like consolidation, glass-round opacity and mix pattern.

8.3. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs as detailed in this Section of the protocol.

8.3.1. **Definitions of Adverse Event (AE)**

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the patient to have occurred, or a worsening of a pre-existing condition. An adverse event may or may not be related to the study treatment.

AEs will be elicited through direct questioning and subject reports. Any abnormality in physical examination findings or laboratory results that the investigator believes is clinically significant (CS) to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should not be recorded as an AE.

8.3.2. **Definition of Serious Adverse Events**

A SAE is defined as any AE that:

- Results in death
- Is life threatening (the subject is at immediate risk of dying from the adverse experience)
- Requires subject hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse effect when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3. Classification of an Adverse Event

8.3.3.1. Severity of Event

The guidelines outlined in CTCAE v5.0 will be used for assessing the intensity of the event. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at http://evs.nci.nih.gov/ftp1/CTCAE.

Table 5. CTCAE v5.0 General Guidelines

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

†Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

-Common Terminology Criteria for Adverse Events (CTCAE), v5.0: November 27, 2017

8.3.3.2. Causality Assessment

AEs will be assigned a relationship (causality) to the study treatment. The Investigator will be responsible for determining the relationship between an AE and the study treatment. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study treatment. Relationship of AEs to study treatment will be classified as follows:

1. **Definitely related**: This category applies to those AEs that the Investigator feels are incontrovertibly related to the study treatment. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it follows a known response pattern to treatment with the study treatment.
2. **Probably related:** This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study treatment. An AE may be considered probable if or when (must have three): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.
3. **Possibly related**: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are judged unlikely but cannot be ruled out with certainty to the study treatment. An AE may be considered possible if or when (must have two): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.
4. **Remotely related**: In general, this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged likely to be unrelated to the study treatment. An AE may be considered unlikely if or when (must have two): (1) it does not follow a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It does not follow a known response pattern to treatment with the study treatment.
5. **Unrelated**: This category applies to those AEs which, after careful consideration at the time they are evaluated, are clearly and incontrovertibly due to extraneous causes (disease,

environment, etc.) and determined with certainty to have no relationship to the study treatment.

8.3.3.3. **Expectedness**

Medical Monitor will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the information described in the Investigator Brochure.

Refer to the Investigator Brochure for the expected/anticipated events.

8.3.4. **Reporting of Adverse Events**

Report initiation for all AEs and SAEs will begin at the time of randomization and continue until the end of final study visit. All events will be followed to resolution or until the subject completes the study. A final assessment of outcome will be made at that time.

All AEs must be recorded in the subject's study records. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is considered to be a SAE (see **Section 8.3.2**), the impact the event had on study treatment (see **Section 8.3.4.1**), the Common Terminology Criteria for Adverse Events (CTCAE) grade (intensity) of the event (see **Section 8.3.3.1**), the causality of the event (see **Section 8.3.3.2**), whether treatment was given as a result of the event (see **Section 8.3.4.2**), and the outcome of the event. (see **Section 8.3.4.3**)

8.3.4.1. **Impact on Study Treatment**

The impact the event had on the study treatment will be assessed as either: dose increased, dose not changed, dose rate reduced, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown. The "not applicable" assessment will be used only when the subject is no longer in the Treatment Phase of the protocol.

8.3.4.2. **Treatment Given as a Result of the Event**

The event impact in terms of treatment provided will be as either: none, medication administered, non-drug therapy administered, surgery performed, hospitalization, or other (with a specification).

8.3.4.3. **Outcome Assessment**

The outcome of the event will be assessed as either: fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, or unknown. Only one AE per subject is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given subject, only the primary cause of death will have an outcome of death.

8.3.5. **Reporting of Serious Adverse Events (SAE)**

The Investigator is required to report all SAEs that occur during the time period specified in **Section 8.3.4**. The sponsor or its designated representative shall be notified within 24 hours of the Investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to the sponsor must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator

is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to the sponsor in accordance with the time frames for reporting specified above. In addition, an investigator may be requested to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or its designated representative.

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

8.3.6. **SAE Follow-Up**

All subjects experiencing an SAE, including the discontinued subjects, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator (i.e., recovery, return to baseline status, no further improvement expected, or death).

For each SAE indicated as an unresolved event on the initial report, regardless of whether the subject completed the study or withdrew, the site should submit a follow-up report with updated information.

9. STATISTICAL ANALYSIS

This section presents general information about statistical considerations and concepts and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions that will be used in this study will be in a separate document; i.e., the Statistical Analysis Plan (SAP).

9.1. TREATMENT GROUPS

There will be two treatment groups in the study:

- **Arm A:** Best supportive and/or standard of care in combination with CX-4945 1000 mg BID PO or
- **Arm B:** Best supportive/standard of care

9.2. DESCRIPTION OF STUDY OUTCOMES (ENDPOINTS)

For description of study outcomes see the Objectives and endpoints in Section 3

9.2.1. Safety Measures:

- Incidence and severity of adverse events (AEs)
- Incidence of serious adverse events (SAEs)
- Incidence of AEs and SAEs leading to discontinuation of study medication.
- Changes in blood chemistry (including electrolyte abnormalities), hematology and coagulation parameter results
- Changes in vital signs including temperature, pulse, respiratory rate, systolic and diastolic blood pressure
- Changes in physical examination results
- Changes in electrocardiogram (ECG) results

9.3. SAMPLE SIZE DETERMINATION AND RATIONALE

A total of 40 subjects will be randomized 1:1 in this study. The sample size is based on clinical judgment. No statistical power calculation will be used to establish the sample size for this proof-of-concept study.

9.4. RANDOMIZATION

The randomization will use block size of 2 or 4 with a 1:1 ratio of CX-4945 in addition to SoC/supportive care group and SoC/supportive care alone group to ensure balanced distribution of subjects. An individual (pharmacy staff), independent of the clinical trial team, will develop the randomization schedules. Subjects who have provided written informed consent and have met all

the inclusion criteria and none of the exclusion criteria will be randomized to one of the treatment groups.

9.5. BLINDING

This is an open label study.

9.6. INTERIM ANALYSIS

No Interim Analysis (IA) is planned for this study.

9.7. GENERAL STATISTICAL CONSIDERATIONS

All collected study data will be presented in subject data listings. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented by treatment group for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables.

9.7.1. Analysis Populations

9.7.1.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all randomized subjects. This population will be used as the primary analysis population for analysis of the primary and secondary efficacy endpoints.

9.7.1.2. Per Protocol Population

The Per Protocol (PP) population is defined as the set of subjects who meet the ITT Population requirements and are not associated with any major protocol violations. This population will be identified before the database lock. This population will be used as the supportive analysis population for analysis of the primary and secondary efficacy endpoints.

9.7.1.3. Safety Population

The Safety population is defined as any subject receiving at least one dose of CX-4945 or standard of care treatment after randomization. This population will be used for the analysis of safety parameters.

9.7.2. Covariates

For efficacy analyses important prognostic factors that need adjustment will be specified in the Statistical Analysis Plan (SAP) for the study

9.7.3. Missing Data

The method for handling missing data will be included in the statistical analysis plan. Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been randomized in the study to minimize missing data. However, in the event when there is missing data the following imputation methods will be used.

For activity/efficacy evaluations, multiple imputation methods will be used to handle missing data and will be detailed in the Statistical analysis Plan (SAP). This imputation method is a robust method to impute potential missing measurements.

9.8. ANALYSIS METHODS

A statistical analysis plan (SAP) will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the data from this trial.

9.8.1. Subject Disposition

The disposition of all subjects who signed an ICF will be provided. The number of subjects screened, screen failed, received at least one treatment, completed, and discontinued during the study, as well as the reasons for all discontinuations will be summarized by treatment group. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

9.8.2. Demographic and Baseline Characteristics

Demographics and baseline characteristics including medical history, prior and concomitant medications/therapies will be summarized by treatment group using appropriate descriptive statistics.

9.8.3. Concomitant Medications/Therapies

Concomitant medications/therapies will be summarized separately for the Safety population. It will be coded to matching Anatomic Therapeutic Classification codes using the most recent version of the WHO Drug Dictionary. Descriptive summaries by treatment group will be prepared using the coded term.

9.8.4. Study Outcome Assessment

For continuous variables data will be summarized by treatment using n, mean, SD, minimum and maximum values. For categorical variables data will be summarized by treatment using frequency and percentage. No inferential statistics are planned. The Safety Population will be used for the analysis of safety outcomes.

9.8.4.1. Efficacy Analysis

Analysis of the efficacy endpoints will be summarized according to the variable type and will be detailed in the SAP:

- Continuous data:
    - If the normality assumption is met, Analysis of Covariance (ANCOVA) would be used.
    - If the normality assumption is not met, a non-parametric method or a rank – ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.
- Categorical data summaries will be based on logistic regression or proportional odds model will be used.
- Time-dependent data: Cox proportional hazards model will be used to analyze time dependent data and Kaplan-Meier methods will be used to depict the time to event data.

9.8.4.2. **Supportive Analysis**

To assess the consistency of the Primary Analysis results, supportive analysis will be conducted using the Intent to Treat (ITT) and Per Protocol (PP) populations. Statistical methodology for the supportive analyses will be the same as that of the primary analysis, with the exception of the analysis population used.

9.8.4.3. **Safety Summaries**

Adverse Events

Adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- Overall (i.e., regardless of severity or relationship to treatment);
- By intensity (mild, moderate, severe, life threatening or death);
- By causality (definitely, probably, possibly, remotely or unrelated);
- By impact on study treatment (dose increased, dose not changed, dose rate reduced, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown).

In addition, separate summaries of serious adverse events, and adverse events resulting in discontinuation of study treatment will be presented.

Clinical Laboratory Data

All laboratory values will be listed. Laboratory measurements will also be summarized and presented by treatment group and time point.

ECG

All ECG values will be listed. ECG measurements will also be summarized and presented by treatment group and time point.

Vital Signs

All vital sign findings will be listed and/or summarized.

Physical Examination

All physical examination findings will be listed and/or summarized.

9.9. DMC PERIODIC SAFETY REVIEW

An independent Data Monitoring Committee (DMC) established by the site will be used during the study to ensure subject safety and trial integriry and also to provide support in assessment of any new possible safety risks imposed by the COVID-19 public health emergency on patient safety and its possible impact of protocol implementation.

The DMC will review the listings of adverse events, protocol deviations, and an enrollment summary. The first formal safety review will occur after the first 3 patients randomized to the CX4945 treatment (Arm A) complete their treatment course. The study accrual will not be interrupted for the scheduled safety reviews, if no specific study-related safety concerns are raised by the Sponsor-Investigator of DMC members. Subsequent periodic safety review will be scheduled as prespecified in the DMC charter. The DMC or Sponsor-Investigator may request an ad hoc meeting for any reason, including a significant unexpected safety event, follow-up of observations during a planned DMC meeting, high enrollemnt rate, or a report external to the study, such as publication of study results from a competing product. The DMC will communicate major safety concerns and recommendations regarding study modification or termination to Sponsor-Investigator. Recommendations are not legally binding but require consideration and a formal written response from the Sponsor-Investigator. Further details are provided in the DMC charter.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Subjects will be identified on study records by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject.

The local IRB, FDA, the monitors, auditors and personnel authorized by the Investigator/Sponsor are eligible to review the medical and research records related to this study as part of their responsibility to protect human subjects in clinical research. They will be given direct access to source data and documentation (e.g., medical charts/records, printouts etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy. The Investigator will be required to ensure access while remaining compliant with institutional requirements.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. MONITORING REQUIREMENTS

The Investigator/Sponsor should be aware that the study site and subject records may be inspected by the FDA or other regional regulatory authority.

11.2. MODIFICATION OF PROTOCOL

The Investigator/Sponsor will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator/Sponsor's IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject; or
2. When the modification does not involve the subject's participation in the trial.

An amendment may also require modification of the informed consent form.

11.3. REPORTING PROTOCOL DEVIATIONS

The Investigator/Sponsor is obligated to follow the protocol without departure from the requirements written in the protocol. The Investigator/Sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved.

11.3.1. Major Protocol Deviation or Violation

A major protocol deviation or violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or wellbeing and/or the completeness, accuracy and reliability of the study data. Examples of this include:

- Failure to obtain informed consent prior to initiation of study-related procedures
- A research subject does not meet the protocol's eligibility criteria but was enrolled
- A research subject received the wrong treatment or incorrect dose.
- A research subject met withdrawal criteria during the study but was not withdrawn.
- A research subject received a prohibited concomitant medication.
- Failure to treat research subjects per protocol procedures that specifically relate to primary outcome measures.
- Changing the protocol without prior IRB approval.

- Multiple minor violations of the same nature after multiple warnings.

11.3.2. **Minor Protocol Deviation or Violation**

A minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which DOES NOT have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Examples of this include:

- Follow-up visits that occurred outside the protocol required time frame because of the participant's schedule.
- Blood samples obtained at times close to but not precisely at the time points specified in the protocol.

12. ETHICS AND REGULATORY REQUIREMENTS

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, GCP, 21 CFR, ICH E6, HIPAA regulations in 45 CFR Part 164 (US only), and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without the prior review and approval of the IRB, except when the modification does not involve the subject's participation in the trial or where it may be necessary to eliminate an immediate hazard to a research subject. In the latter case, the change will be reported to the IRB as soon as possible, according to IRB regulations.

Additionally, the study product used in this study is manufactured, handled and stored in accordance with applicable GMP. The study product provided for this study will be used only in accordance with this protocol.

12.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

The Investigator/Sponsor will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, informed consent form, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned document. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Investigator will be made to the IRB/IEC as required by local and applicable government regulations. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the modification does not involve the subject's participation in the trial.

12.2. INVESTIGATOR'S RESPONSIBILITIES

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations. Information regarding the study sites participating in this study that cannot comply with these standards will be documented.

12.3. SUBJECT INFORMED CONSENT REQUIREMENTS

All subjects participating in this study will be given written and oral information about the study by the Investigator and/or designee, in a language understandable by the subject. Written informed consent will be obtained from each subject prior any procedures or assessments that would not otherwise be required for the care of the subject are done. After the objectives, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

The written Informed Consent Form (ICF) will be in compliance with CFR 21 Part 50.27 and GCP guidelines. A copy of the ICF to be used will be submitted by the Investigator/Sponsor to the IRB/IEC for review and approval prior to the start of the study. The original signed ICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject's medical record, if allowed by institutional policy.

13. DATA HANDLING AND RECORD KEEPING

13.1. RECORDING AND COLLECTION OF DATA

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the Investigator(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study.

The Investigator will maintain a confidential list of study subjects that will include each subject's study number, name, date of birth, and unique hospital identification number if applicable. A notation will be made in the subject's case history/medical chart that he/she is participating in a clinical study and has provided a signed and dated ICF as well as a release for protected health information as required by local policies. The Investigator must also maintain a separate screening log of all the subjects screened for participation in the study; it should include gender, age, eligibility status, reason for ineligibility, if applicable; and study allocated subject number, if applicable.

13.2. ARCHIVING

All study documentation at the Investigator site will be archived in accordance with ICH GCP E6 and the Investigator/Sponsor's quality standards and SOPs.

The Investigator will maintain all research records, reports, and case history reports for a period of two (2) years after regulatory approval of the investigational product. If no application is filed or if the application is not approved, records must be maintained for two (2) years after all investigations have been completed, terminated or discontinued and the FDA has been notified.

These documents should be retained for a longer period however, if required by the applicable regulatory requirements (as per GCP 5.5.11).

Study records are subject to inspection by applicable health and regulatory agencies at any time. Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., subject's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study)
- Signed protocols and protocol amendments
- Laboratory results, ranges, and certifications
- IP and accountability records
- Study personnel signature log

- Monitoring logs
- Investigator and sub-investigator CVs
- Signed informed consent and protected health information consent forms
- Subject screening
- SAE reports
- IRB approval and re-approval letters
- Completed quality of life questionnaire
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

Study records are subject to inspection by applicable health and regulatory agencies at any time.

14. PUBLICATION PLAN

All information supplied by the Investigator/Sponsor and Senhwa in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, clinical protocol, case report forms and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of the Investigator/Sponsor and Senhwa, shall not be disclosed to others without the written consent of the Investigator/Sponsor and Senhwa, and shall not be used except in the performance of this study.

It is understood by the Investigator that the Sponsor will use the information collected in this clinical trial in connection with the development of the Investigator/Sponsor and Senhwa. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities.

15. REFERENCES

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16. APPENDIX

16.1. APPENDIX 1: EQ-5D-5L QUESTIONNAIRE

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

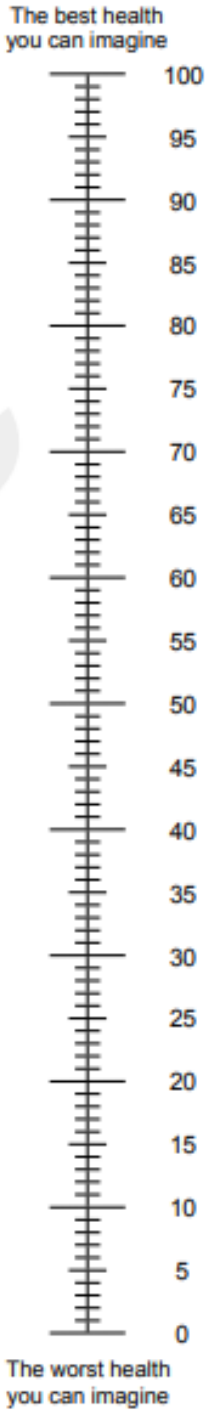
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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16.2. APPENDIX 2: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.03

For complete detailed information please refer to the link below:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf