A Phase II, Randomized and Controlled Investigator Initiated Trial Evaluating Safety, Pharmacokinetics and Clinical Benefit of Silmitasertib (CX-4945) in Outpatient Adult Subjects with Moderate Coronavirus Disease 2019 (COVID-19)

Protocol Number:	**CX4945-AV01-IIT**
Protocol Amendment:	**1.0**
Date:	**11-May-2021**
Study Product:	**Silmitasertib (CX-4945)**
Sponsor-Investigator:	**Dr. Chris Recknor, MD** Center for Advanced Research & Education 2350 Limestone Pkwy Gainesville, GA 30501
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PROTOCOL APPROVAL PAGE

Protocol Number:	**CX4945-AV01-IIT**
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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

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**CX4945-AV01-IIT**
Protocol Amendment:	**1.0**
Date:	**11-May-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.

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Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	11 May 2021	The primary purpose of the amendment is to add 1-2 additional sites to boost enrollment and incorporate feedback received from the United States (US) Food and Drug Administration (FDA). In addition, clarifications, reconciliations, administrative and typographical modifications were made. 1. "Single-center study" was replaced by "Multicenter study" throughout the protocol. 2. As study population is outpatients with moderate COVID-19, a Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials will be used for grading of AEs associated with systemic (general) abnormalities, vital signs, illnesses and lab abnormalities instead of CTCAE v.5.0 (FDA recommendation). Full guidelines may be obtained at https://www.fda.gov/media/73679/download . 3. Section 1.1. SYNOPSIS: • Study Description: It was clarified that CX-4945 neither impacts on the effectiveness of other antiviral drugs nor contributes to the emergence of viruses with reduced susceptibility to the drug, since CX-4945 targets the host protein kinase. • Study Description. Number of enrolled patients was changed from "20" to "approximately 20" to add flexibility in case any patients to be replaced due to protocol violation or discontinue the study prior to the first dose, etc. • Secondary Objectives and Endpoints: The secondary objective to evaluate time to clinical recovery measured by time to resolution of clinical

		signs and symptoms was split to two objectives measured separately by duration of clinical signs and duration of clinical symptoms correspondingly (FDA recommendation). • Secondary Objectives and Endpoints: The secondary objective to evaluate CX-4945 PK was updated to clarify that PK samples will be collected from the first four patients randomized to treatment arm A. Further PK collection is not required, as enough data have been collected in two CX-4945 studies to proceed with PK analysis. • Secondary Objectives and Endpoints (other clinical benefit of treatment with CX-4945): evaluation of disease progression and health improvement measured by the ordinal 8- Point Clinical Progression Outcome Scale was clarified. • Secondary Objectives and Endpoints (other clinical benefit of treatment with CX-4945): Outcome measure for changes of SpO2 was updated to number of days to normalization of oxygen saturation (categorized as <96% versus ≥96%). • Study Duration was changed from 5 months to 12 months due to enrollment challenges. 4. Section 1.3: SHEDULE OF ACTIVITIES • Assessment for the requirement of mechanical ventilation, ECMO, non-invasive ventilation, or high-flow nasal cannula oxygen delivery was deleted as it was the same as clinical status assessment using the ordinal 8- Point Clinical Progression Outcome Scale. • PK collection was removed from the Schedule of Activities (SOA). PK samples will not be collected anymore, as enough data have been collected in two CX-4945 studies to proceed with PK analysis. • Numbers of footnotes were reconciled

		• Footnote 14: It was clarified that Follow-up visits (Day 28, Day 45, and Day 60) may be performed via phone or telehealth only for recovered patients. • Day 2, Day 15, Day 16 and Day 17 visits were deleted from the SOA as these visits are required only for patients participating in the PK study. PK collection is not required anymore, as enough data have been collected to proceed with PK analysis. 5. Section 2.1: STUDY RATIONALE • Study Rationale was updated in accordance with the recent COVID-19 Treatment Guidelines of 8-Apr-21 (https://www.covid19treatmentguidelines.nih.gov). 6. Section 2.4: RISK/BENEFIT ASSESSMENT • It was added that CX-4945 does not impact the effectiveness of other antiviral drugs or contribute to the emergence of viruses with reduced susceptibility to the drug, since CX-4945 is an inhibitor of the host protein kinase. 7. Section 3: STUDY OBJECTIVES AND ENDPOINTS • The same changes were made in Section 3 as listed above under Item 3, bullets 4, 5, 6 and 7. 8. Section 4.1: OVERALL DESIGN • Addition to SOC: Patients progressed on treatment with monoclonal antibodies can be enrolled, if meet eligibility criteria. 9. Section 5.1.1: INCLUSION CRITERIA • The inclusion criterion #2: a timeframe of 7 days before Day 1 was specified for the positive screening PCR test required for eligibility evaluation. • The inclusion criterion #3: the names of the symptoms were aligned with those in the proposed patient-reported outcome (PRO) instrument (FDA recommendation).

		• The inclusion criterion #9 was added: Patient must agree not to participate in another clinical trial for the treatment of COVID-19 during the study period until disease progression, hospitalization, withdrawal from study treatment or 28 days after the start of the study, whichever occurs first. 10. Section 5.1.2: EXCLUSION CRITERIA • The exclusion criterion #5 of "concomitant treatment with another investigational drug from Day 1 through Day 28" was revised to "concomitant treatment with another investigational drug" as it should not be applied after treatment initiation (FDA recommendation). • The exclusion criterion #7 was added: Any active or recurring clinically significant hepatic disease (FDA recommendation). 11. Section 6.1.5: CX-4945 DOSE MODIFICATION • Table 3, CX-4945 Dose Modification and Management for Potential Toxicities: Standardized toxicity grading scale (CTCAE v.5.0) was modified to Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials https://www.fda.gov/media/73679/download (FDA recommendation) • Reasons for dose discontinuation were listed 12. Section 7: STUDY COMPLETION OR DISCONTINUATION • This Section was revised to reconcile discrepancies and clarify difference between study discontinuation and withdrawal from treatment (FDA recommendation). 13. Section 8.2.2: EFFICACY/ANTI-VIRAL ACTIVITY ASSESSMENT • COVID-19-related symptoms and signs will be evaluated separately for recovery assessment (FDA

		recommendation). Section 8.2.2.1 describes COVID-19-related symptoms assessment. Section 8.2.2.2. describes clinical signs assessment. Heart rate was added to clinical sign assessment (section 8.2.2.2). It was added that any abnormal signs or symptoms not related to COVID-19 and caused by other conditions documented in medical history and started before COVID-19 will not be included to recovery assessment. The patient can be considered as recovered, when these symptoms return to the previous (pre-COVID-19) values. 14. Section 8.3.3.1: SEVERETY OF AEs • As study population is outpatients with moderate COVID-19, a standardized toxicity grading scale was modified to reflect the study population. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials will be used for grading of AEs associated with systemic (general) abnormalities, vital signs, illnesses and lab abnormalities instead of CTCAE v.5.0 (FDA recommendation). Full guidelines may be obtained at https://www.fda.gov/media/73679/download . 15. Section 9.2: DESCRIPTION OF STUDY OUTCOMES • Duplicate information has been removed and reference to Section 1.1. and Section 3 is added. 16. Section 9.4: RANDOMIZATION • WebView IWRS has been removed as it not applicable for this study.

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1. PROTOCOL SUMMARY

1.1. SYNOPSIS

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<tr><td>Study Description:</td><td colspan="2">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 affects many vital processes in host cells contributing to dysregulated host immune response, viral survival, replication and spread to nearby cells. CX-4945 demonstrated anti-viral and anti-inflammatory efficacy in COVID-19 in vitro studies and remarkable clinical benefits under emergency IND authorization. As CX-4945 is an inhibitor of the host protein kinase CK2, it does not impact on the effectiveness of other antiviral drugs or contribute to the emergence of viruses with reduced susceptibility to the drug.

This is a Phase II multicenter, open-label, randomized two-arm parallel-group controlled study in approximately 20 subjects to evaluate safety and explore putative clinical benefits of CX-4945 1000 mg BID dose in patients with moderate COVID-19. It will be a two-arm trial comparing the SOC/supportive care alone to the SOC/supportive care in combination with CX-4945(allocation ratio 1:1).</td></tr>
<tr><td>Primary Objective and Endpoints:</td><td>Primary Objective</td><td>Primary Endpoint</td></tr>
<tr><td></td><td>To assess safety and tolerability of CX-4945 administered orally twice daily to patients with moderate COVID-19</td><td>Adverse events occurring from randomization (Day 1) to Day 60 (including vital signs, physical findings, clinical laboratory, and ECG results) as characterized by type, frequency, severity [as graded by Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (https://www.fda.gov/media/73679/download)], , timing, seriousness, and relationship to study therapy.</td></tr>
<tr><td>Secondary Objectives and Endpoints:</td><td>Secondary Objectives</td><td>Secondary Endpoints</td></tr>
<tr><td></td><td>To compare time to normalization of COVID-19-related</td><td>Number of days from Randomization (Day1) to the day when the following clinical signs are back to normal (as evaluated at every visit during the treatment period (Day</td></tr>
</table>

	clinical signs in CX-4945 treatment arm versus the control arm.	1, Day 4, Day 8, Day 11 and Day 14) and at Follow-up visits (Day 28 and Day 45): o Fever is ≤36.6°C from axillary site, or < 37.2°C from oral site or < 37.8°C from rectal or tympanic site o Respiratory rate is < 20 breaths per minute o SpO2 ≥ 96% in room air without shortness of breath or dyspnea caused by COVID-19 o Heart rate < 90 beats per minute *Note: If some signs listed above were caused by other conditions documented in the medical history and started before COVID-19, the patient can be considered as recovered, when these signs return to the previous (pre-COVID-19) values.*
	To compare duration of COVID-19-Related clinical symptoms in CX-4945 treatment arm versus the control arm.	Number of days from randomization (Day1) to the day when: • No key COVID-19-related symptoms scored higher than 1 as documented using a Patient Reported Outcome (PRO) instrument (a Patient Diary for Assessment of Common COVID-19-Related Symptoms – see Appendix 3), evaluated daily from Day 1 through Day 14 and at Day 28 and Day 45. *Note: Each symptom is scored individually using the following response options and scoring values:* o *Items 1–18: None = 0; Mild = 1; Moderate = 2; and Severe = 3* o *Items 19 and 20: Not at all = 0; 1–2 times = 1; 3–4 times = 2; 5 or more times = 3*

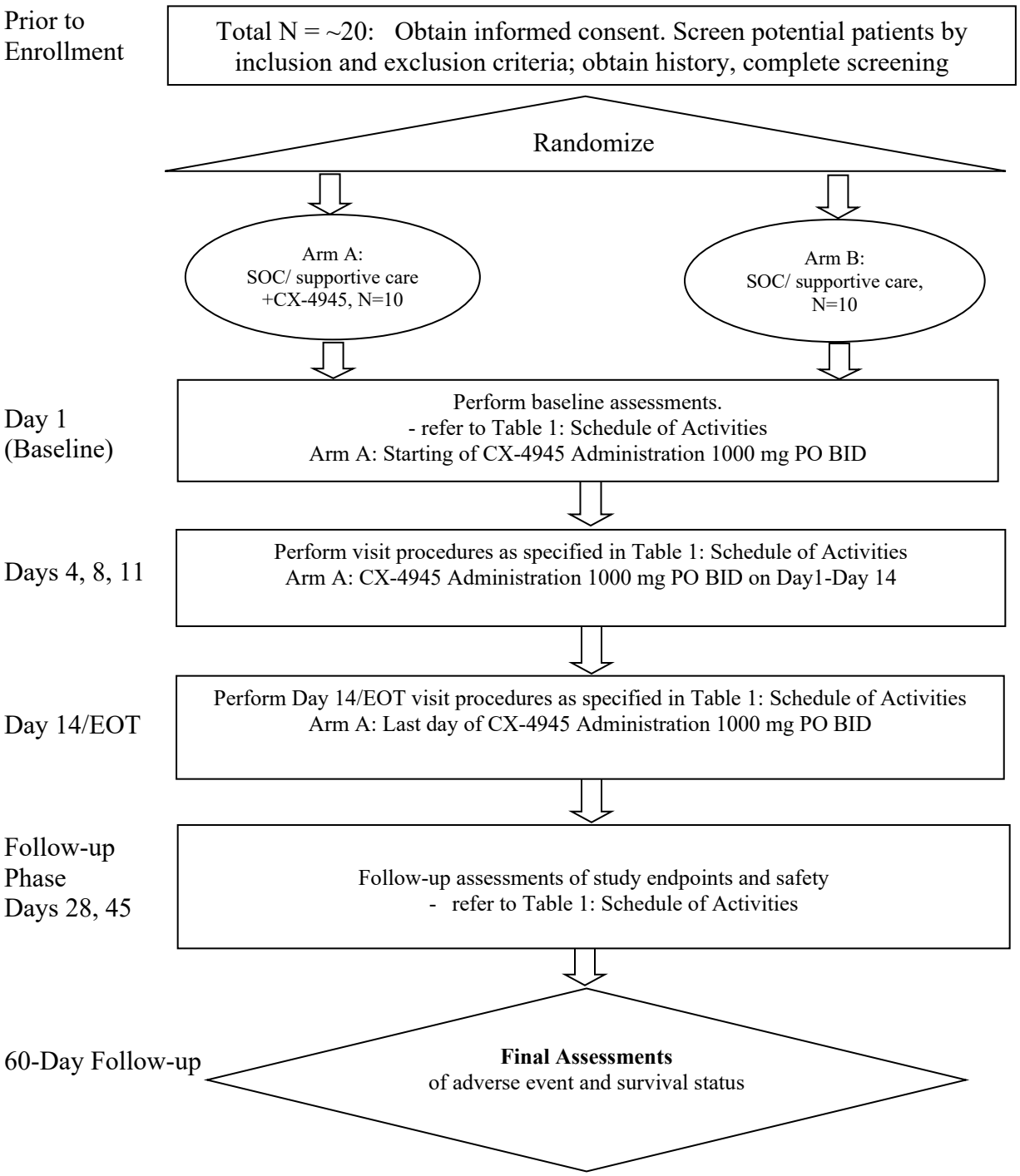
		○ *Items 21-22: The same as usual = 0, Less than usual = 1, NO sense of smell/taste = 2.* *Note: If some symptoms were caused by other conditions documented in the medical history and started before COVID-19 (e.g. insomnia), the patient can be considered as recovered, when these symptoms return to the previous (pre-COVID-19) value.*
	To evaluate preliminary evidence of anti-viral activity of CX-4945 as compared to the control arm.	• Change in virologic measure: • Proportion of patients with conversion of positive RT-PCR to negative RT-PCR from randomization (Day 1) through Day 28. • Time to SARS-CoV-2 viral clearance measured as number of days from positive RT-PCR collected at randomization (Day1) to negative RT-PCR. • Quantitative changes in viral load from randomization (Day 1) to Day 28. *Note: RT-PCR/viral load tests will be performed at randomization (Day 1) and then on Day 8, Day 14 and Day 28.*
	To evaluate the PK of CX-4945 when given at 1000 mg BID PO (Treatment Arm A only)	• Plasma sample for PK assessment are collected at the following timepoints from the first four patients randomized to treatment arm A: ○ Day 1: pre-dose, 1, 2, 3, 6 and 24 hours post Day 1 morning dose. ○ Day 14: pre-dose, 1, 2, 3, 6, 24, 48 and 72 hours post Day 14 morning dose.

		Note: The following PK parameters will be calculated: Cmax, Tmax, AUC_{0-T}, AUC_{0-6}, and $T_{1/2}$
	To evaluate other Clinical Benefit of treatment with CX-4945 relative to the control arm	• All-cause mortality status – the number of deaths occurred in each treatment group from Randomization (Day 1) through Day 60. • Number of respiratory failure (i.e., need for mechanical ventilation, ECMO, noninvasive ventilation, or high-flow nasal cannula oxygen delivery) occurred in each treatment group from Randomization (Day 1) through Day 45. • Number of patients hospitalized in each treatment arm from Randomization (Day 1) to Day 45 • Number of days to normalization of oxygen saturation level measured by pulse oximeter at Randomization (Day 1), Day 4, Day 8, Day 11, Day 14, Day 28 and Day 45 and categorized as <96% versus ≥96%.Proportion of patients with disease progression or improvement in health status occurring from Randomization (Day 1) to Day 28. Disease progression is defined as change in patient health status assessment from item 7 to items 1- 6 and health improvement -as change from item 7 to item 8, evaluated by the ordinal NIAID 8-Point Clinical Progression Outcomes scale collected at every visit from Day 1 through Day 45. The 8-category 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. • Changes in EQ-D5-5L (used as an indicator of symptom improvement) from randomization (Day 1) to Day 8, Day 14 and Day 28.
	To evaluate changes in inflammatory markers	• Changes in plasma IL-6 level from randomization (Day 1) to Day 4, 8, 11, and 14. • Changes in CRP, LDH, CPK, ferritin, D-dimer from randomization (Day 1) to Day 4, 8, 11, and 14.
Study Population:	This study will enroll male and non-pregnant female patients ≥ 18 years of age with moderate COVID-19. Approximately 20 outpatients will be equally randomized in two treatment arms.	
Phase:	II	
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:	12 months (from study initiation until completion of data analyses)	

Patient 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 = ~20: Obtain informed consent. Screen potential patients by inclusion and exclusion criteria; obtain history, complete screening
Randomize
Arm A: SOC/ supportive care +CX-4945, N=10
Arm B: SOC/ supportive care, N=10
Day 1 (Baseline)
Perform baseline assessments.
- refer to Table 1: Schedule of Activities
Arm A: Starting of CX-4945 Administration 1000 mg PO BID
Days 4, 8, 11
Perform visit procedures as specified in Table 1: Schedule of Activities
Arm A: CX-4945 Administration 1000 mg PO BID on Day1-Day 14
Day 14/EOT
Perform Day 14/EOT visit procedures as specified in Table 1: 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 Table 1: 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					Follow-Up [14]		
Day	SV	Day 1 (Baseline)	Day 4	Day 8	Day 11	Day 14 (EOT)	Day 28	Day 45	Day 60
Window Period	D-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								
Patient 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 COVID-19-related Symptoms [6]	X	Assessed Daily from Day 1-Day 14					X	X	
EQ-D5-5L		X		X		X	X		
Clinical Status - Ordinal 8-point Scale Assessment	X	X	X	X	X	X	X	X	
Pulse Oxygen Saturation (SpO2)	X	X	X	X	X	X	X	X	
ECG	X					X			
Laboratory Tests:									
Hematology [7]	X	X	X	X	X	X	X	X	
Blood Chemistry [8]	X	X	X	X	X	X	X	X	
Coagulation [9]	X	X	X	X	X	X	X	X	
Serum/Urine Pregnancy Test [10]	X					X			
Urinalysis [11]	X	X	X	X	X	X	X	X	
IL-6 levels		X	X	X	X	X			
Nasopharyngeal Swab Sample Collection [12]	X	X		X		X	X		
Randomization [13]		X							

IP Administration (Arm A only)		Arm A: CX-4945 1000 mg BID (Day 1-Day14)							
SOC/Supportive care (Arm A and Arm B)	X (as needed)								
Mortality Status		X	X	X	X	X	X	X	X
Concomitant Medications	X	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] Common COVID-19-Related Symptoms (see Appendix 3) should be assessed by patients daily from Day 1 through Day 14/EOT and at Day 28 and Day 45 Follow-up visits..

[7] Hematology: Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total and differential count, Absolute Neutrophil Count (ANC) and platelets.

[8] Blood Chemistry:

- 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, total calcium and bicarbonate
- Other: Creatine phosphokinase (CPK), C-reactive protein (CRP), serum ferritin, d-dimer

[9] Coagulation: Prothrombin time (PT) and International Normalized Ratio (INR)

[10] ONLY performed on women of childbearing potential.

[11] 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.

[12] Swabs will be used for RT-PCR and quantitative virologic testing:

- Positive RT-PCR collected within 7 days before Day 1 is required at screening for patient eligibility evaluation.
- Nasopharyngeal swab for RT-PCR and viral load assessment should be collected at Day 1, 8, 14 and 28 visits. Samples are to be stored at -70°C and shipped to the Fulgent lab twice a month.

[13] **Randomization:** Patient number and treatment arm allocation can be performed on Day 1

[14] For recovered patients Follow-up visits may be performed via phone or telehealth, as appropriate

2. INTRODUCTION AND BACKGROUND

2.1. STUDY RATIONALE

The COVID-19 pandemic is an ongoing global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified in December 2019 in Wuhan, China. As of 2 April 2021, more than 129 million cases have been confirmed, with more than 2.82 million deaths attributed to COVID-19. Symptoms of COVID-19 are highly variable, ranging from none to life-threatening illness. The virus spreads mainly through the air from person to person. Common symptoms include headache, loss of smell and taste, nasal congestion and rhinorrhea, cough, muscle pain, sore throat, fever, diarrhea, and breathing difficulties. Most people develop mild to moderate symptoms.

The COVID-19 Treatment Guidelines Panel (https://www.covid19treatmentguidelines.nih.gov) that includes representatives from federal agencies, health care and academic organizations, and professional societies, continues to review the most recent clinical data to provide up-to-date treatment recommendations for clinicians who are caring for patients with COVID-19. Remdesivir, an antiviral agent, is currently the only drug that is approved by the FDA for the treatment of COVID-19, but it is recommended for use only in hospitalized patients who require supplemental oxygen. Dexamethasone, a corticosteroid, has been found to improve survival in hospitalized patients who require mechanical ventilation, but it is not recommended for use in outpatients with moderate disease. Preliminary data suggests that outpatients may benefit from receiving anti-SARS-CoV-2 monoclonal antibodies early in the course of infection. The Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) for certain anti-SARS-CoV-2 monoclonal antibodies for the treatment of outpatients with mild to moderate COVID-19. However, the COVID-19 Treatment Guidelines includes information on the various reported SARS-CoV-2 variants and the potential impact of mutations on in vitro susceptibility to different anti-SARS-CoV-2 monoclonal antibodies. Because of these limitations, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using anti-SARS-CoV-2 monoclonal antibody combinations only to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression Ongoing clinical trials will provide further evidence information about the safety and efficacy of these agents.

Despite some drugs demonstrating good efficacy, there are a number of patients not responsive to available anti-COVID-19 therapy. There is no specific antiviral treatment recommended for outpatients with moderate COVID-19. Current standards of therapeutic management of outpatients with moderate COVID-19 includes symptomatic and supportive care, such as NSAIDs to relieve symptoms (fever, body aches, cough).

Along with the development of new antiviral drugs, repurposing of existing drugs for COVID-19 treatment has also been accelerated. 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. Therefore, development of an effective antiviral drug for COVID-19 is a global health priority and discovery of novel cellular targets for SARS-CoV-2 has led to novel putative clinical strategies which merit going into clinical research in COVID-19.

2.2. BACKGROUND

[redacted]

[redacted]

Emerging pre-clinical and clinical data and results of independent efficacy evaluation conducted by Utah State University [2] and UCSF COVID-19 research group [1] and Senhwa Biosciences hypothesize that 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 moderate to severe COVID-19, thereby preventing disease progression and improving clinical outcomes. The intended target patient population for treatment with CX-4945 is SARS-CoV-2 positive patients with moderate to severe COVID-19, since in the moderate to 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 COVID-19 pneumonia not responsive to remdesivir, dexamethasone and antibiotics and requiring supplemental oxygen. The patient recovered and was discharged from the hospital within five days of treatment with CX-4945.

2.3. CX-4945

[redacted]

[redacted]

CX-4945 is currently under development in several oncology programs in adults and in children with recurrent/advanced or metastatic cancer. CX-4945 is 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 (basal cell carcinoma) and two ongoing phase II studies (cholangiocarcinoma, medulloblastoma).

[redacted]

2.4. RISKS/BENEFITS ASSESSMENT

CX-4945 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. As CX-4945 is an inhibitor of the host protein kinase CK2, it does not impact the effectiveness of other antiviral drugs or contribute to the emergence of viruses with reduced susceptibility to the drug. Based on the currently available data, the identified or potential risks of the product do not outweigh its identified or potential benefits.

3. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoint
To assess safety and tolerability of CX-4945 administered orally BID to patients with moderate COVID-19	• Adverse events occurring from randomization (Day 1) to Day 60 (including vital signs, physical findings, clinical laboratory, and ECG results) as characterized by type, frequency, severity [(as graded by Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (https://www.fda.gov/media/73679/download)], timing, seriousness, and relationship to study therapy.
Secondary Objectives	**Secondary Endpoints**
To compare time to normalization of COVID-19-related clinical signs in CX-4945 treatment arm versus the control arm.	Number of days from Randomization (Day1) to the day when the following clinical signs are back to normal as evaluated at every visit during the treatment period (Day 1, Day 4, Day 8, Day 11 and Day 14) and at Follow-up visits on Day 28 and Day 45 : • Fever is $\leq$ 36.6°C from axillary site, or < 37.2°C from oral site or < 37.8°C from rectal or tympanic site) • Respiratory rate is < 20 bpm while breathing room air at sea level • SPO $\geq$ 96% in room air without shortness of breath or dyspnea • Heart rate < 90 beats per minute *Note: If some signs listed above were caused by other conditions documented in the medical history and started before COVID-19, the patient can be considered as recovered, when these signs return to the previous (pre-COVID-19) values.*
To compare duration of COVID-19-Related clinical symptoms in CX-4945 treatment arm versus the control arm.	Number of days from Randomization (Day1) to the day when: • No key COVID-19-related symptoms scored higher than 1 as documented using a Patient Reported Outcome (PRO) instrument (a Patient Diary for Assessment of Common COVID-19-Related Symptoms – see Appendix 3),

	evaluated daily from randomization (Day 1) through Day 14 and at Day 28 and Day 45. *Note: Each symptom is scored individually using the following response options and scoring values:* o *Items 1–18: None = 0; Mild = 1; Moderate = 2; and Severe = 3* o *Items 19 and 20: Not at all = 0; 1–2 times = 1; 3–4 times = 2; 5 or more times = 3* o *Items 21-22: The same as usual = 0, Less than usual = 1, NO sense of smell/taste = 2.* *Note: If some symptoms were caused by other conditions documented in the medical history and started before COVID-19 (e.g., insomnia), the patient can be considered as recovered, when these symptoms return to the previous (pre-COVID-19) value.*
To evaluate preliminary evidence of anti-viral activity of CX-4945 as compared to the control arm.	Change in virologic measure: • Proportion of patients with conversion of positive RT-PCR to negative RT-PCR from Randomization (Day 1) through Day 28. • Time to SARS-COV-2 viral clearance measured as number of days from positive RT-PCR collected at randomization (Day 1) to negative RT-PCR. • Quantitative changes in viral load from Randomization (Day 1) to Day 28. *Note: RT-PCR/viral load tests will be performed at Randomization (Day 1) and then on Day 8, Day 14 and Day 28.*
To evaluate the PK of CX-4945 when given at 1000 mg BID PO (Treatment Arm A only)	• Plasma sample of CX-4945 are collected at the following timepoints from the first four patients randomized to treatment arm A: o Day 1: pre-dose, 1, 2, 3, 6 and 24 hours post Day 1 morning dose.

	○ Day 14: pre-dose, 1, 2, 3, 6, 24, 48 and 72 hours post Day 14 morning dose. *Note: The following PK parameters will be calculated: Cmax, Tmax, AUC_{0-T}, AUC_{0-6}, and $T_{1/2}$.*
• To evaluate other Clinical Benefit of treatment with CX-4945 relative to the control arm	• All-cause mortality status – the number of deaths occurred in each treatment group from Randomization (Day 1) through Day 60. • Number of patients hospitalized in each treatment group from Randomization (Day 1) to Day 45 • Number of days to normalization of oxygen saturation level measured by pulse oximeter at Randomization (Day 1), Day 4, Day 8, Day 11, Day 14, Day 28 and Day 45 and categorized as <96% versus ≥96%. • Proportion of patients with disease progression or improvement in health status occurring from Randomization (Day 1) to Day 28. Disease progression is defined as change in patient health status assessment from item 7 to items 1- 6 and health improvement -as change from item 7 to item 8, evaluated by the ordinal NIAID 8- point Clinical Progression Outcomes scale – collected at every visit. from randomization (Day 1) through Day 45. An 8-category 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. • Changes in EQ-D5-5L (used as an indicator of symptom improvement) from Baseline (Day 1) to Day 8, 14, 28.
• To evaluate changes in inflammatory markers	• Changes in plasma IL-6 level from Randomization (Day 1) to Day 4, Day 8, Day 11, and Day 14. • Changes in CRP, LDH, CPK, ferritin, D-dimer from randomization (Day 1) to Day 4, Day 8, Day 11, and Day 14.

4. STUDY DESIGN

4.1. OVERALL DESIGN

This is a phase II multicenter, randomized, open-label, 2 arm parallel-group controlled interventional prospective study of CX-4945 in patients with COVID-19. Up to approximately 20 patients will be enrolled into this study. A screening evaluation will occur within 7 days prior to Day 1. At the end of screening all qualified patients will be randomized in a ratio of 1:1 to one of the following two treatment arms:

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

The **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 **standard of care (SOC)** is not pre-specified and 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. Patients progressed on treatment with monoclonal antibodies can be enrolled, if meet eligibility criteria. Active concomitant treatment with other investigational antivirals or immunomodulators are not permitted.

Patients assigned to Arm B will do all the same assessments as Arm A.

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 **Section 6.1.2**.

4.2. JUSTIFICATION FOR DOSE

CX-4945 will be administered BID 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 BID or 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 patients enrolled to date. In total, approximately 115 patients have been treated with 1000 mg BID dosing of CX-4945 in several completed and ongoing studies.

4.3. END OF STUDY DEFINITION

A patient is considered to have completed the study if he or she has completed the Treatment Phase and all Follow-up visits (Days 28, 45, and 60).

Discontinuation from CX-4945 does not mean the withdrawal from the study assessments. Patients 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 20 outpatients with moderate COVID-19. Best supportive and/or SOC alone or in combination with CX-4945 will be given to study patients.

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 with COVID-19 by standard RT-PCR assay within 7 days prior to randomization (Day 1)
3. Outpatients with moderate illness caused by SARS-CoV-2 infection as defined below,

   - Symptoms of moderate systemic illness/infection with COVID-19:
     - **At least two** of the key **COVID-19-related** symptoms with score 2 or higher: cough, sore throat, stuffy or runny nose, shortness of breath, feeling of tightness of chest, feeling of fast heartbeat, low energy or tiredness, muscle cramps, joint pain, chills or shivering, feeling hot or feverish, difficulty in concentration (brain fog), sleep disturbances, headache, dizziness, anxiety, feeling of tingling,nausea (*scoring values: None = 0; Mild = 1; Moderate = 2; and Severe = 3*), vomiting, diarrhea (*scoring values: Not at all = 0; 1–2 times = 1; 3–4 times = 2; 5 or more times = 3),* loss of taste or smell *(scoring values: The same as usual = 0, Less than usual = 1, NO sense of smell/taste = 2)*

     AND

   - Clinical signs indicative of moderate systemic illness/infection with COVID-19
     - **At least one** of the following:
       - Respiratory rate ≥ 20 breaths per minute
       - Heart rate ≥ 90 beats per minute

     AND

- No clinical signs indicative of severe or critical illness severity required hospitalization (see exclusion criterion #1)

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 ≥ 3.0 g/dL
7. 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 the study duration.
9. Patient must agree not to participate in another clinical trial for the treatment of COVID-19 during the study period until disease progression, hospitalization, withdrawal from study treatment or 28 days after the start of the study, whichever occurs first.

5.1.2. Exclusion Criteria

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

1. Any signs indicative of severe or critical illness severity required hospitalization as defined below:
    - Severe COVID-19: Shortness of breath at rest, or respiratory distress, respiratory rate (RR) ≥ 30 per minute, heart rate (HR) ≥ 125 bpm, SpO2≤93% on room air at sea level or PaO2/FiO2<300
    - Critical COVID-19: Respiratory failure required mechanical ventilation, oxygen delivered by high-flow nasal cannula, ESMO; shock or multi-organ dysfunction/failure

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. Chronic diarrhea (excess of 2-3 stools/day above normal frequency)
5. Concomitant treatment with another investigational drug
6. Current use or anticipated need for drugs that are known strong inhibitors or inducers of major CYP enzymes.
7. Any active or recurring clinically significant hepatic disease.

5.2. SCREEN FAILURES

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

If a patient initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the patient 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 treatment Arm A.

Refer to the Investigator's Brochure for more information.

All patients 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 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 patients will be done after confirmation of patient's eligibility. Patients will be allocated randomly into Arm A and Arm B in a 1:1 ratio.

Table 2: Method of Assignment to Treatment

Arm	Supportive Care/SOC	Daily Dose of CX-4945 (mg)	Dose administration BID (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 BID 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 CX-4945. 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 BID, 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 effect in the stomach, so a patient is recommended to take as much as 10 minutes interval between intake of each capsule.

CX-4945 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. CX-4945 Compliance

Site staff will dispense CX-4945 to the patients 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 capsules returned by the patient will be counted, documented, and recorded.

6.1.5. 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 below do not substitute for an investigator's medical judgement. Investigators should always manage their patients according to their medical judgement based on the particular clinical circumstances.

Table 3: CX-4945 Dose Modification and Management for Potential Toxicities (Attributable to CX-4945)

Grade* (attributable to CX-4945)	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 at the Investigator's discretion

** Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials: https://www.fda.gov/media/73679/download*

- **Dose Reduction:** If a dose-response relationship for toxicity is observed, then a reduced dose can be given to the patient. Dose adjustments will be allowed based on the toxicity, efficacy evaluation, and clinical judgment by a physician.
- **Dose Interruption:** Refer to **Table 3** above. Recovery to acceptable levels must occur to allow 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.
    - Withdrawal from the study treatment or participation
    - Pregnancy
    - Significant study therapy non-compliance
    - If any clinical adverse event, laboratory abnormality, or other medical condition or situation occurs that continued treatment under the protocol would not be in the best interest of the patient.

  Discontinuation from CX-4945 does not mean the withdrawal from the study assessments. Patients 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 sites 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 according to the study visit schedule. Any unused product or waste material should be disposed of in accordance with local requirements.

[redacted]

[redacted]

[redacted]

6.3. CONCOMITANT MEDICATION

[redacted]

[redacted]

6.4. CX-4945 Drug Interaction

[redacted]

7. STUDY COMPLETION OR DISCONTINUATION

7.1. PATIENT COMPLETION

A patient 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 CX-4945 does not mean the withdrawal from the study assessments. Patients 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 further participation in the study and loss to follow-up.

7.2. PATIENT WITHDRAWAL FROM PARTICIPATION IN THE STUDY

At any point during the study all patients have the right to withdraw consent from further participation in the study refusing to complete scheduled study assessments and follow-ups without prejudice to future care. If the patient refuses further visits, the patient should continue to be followed unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study-specific evaluations should be performed and no additional data should be collected. The sponsor/investigator may retain and continue to use any data collected before such withdrawal of consent.

Another reason for withdrawal from study is 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.

The reason for withdrawal from the study will be recorded in the subject medical records.

7.3. PATIENT DISCONTINUATION FROM STUDY TREATMENT

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator/sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given investigator site.

All patients who discontinued from study treatment but maintain consent, should remain in the study through the end of the study period for all important safety and anti-viral activity assessments.

Investigators considering patient withdrawal from study treatment should contact the medical monitor prior to such discontinuation. Patients who have study treatment discontinued will continue to be followed, per protocol, whenever possible. If visits to the site are not possible,

subjects can be followed via telehealth or other approaches (telephone calls, e-mails, and texts to ascertain vital status in all patients.

Patients who have study treatment discontinued due to a serious adverse event will be followed until study completion, resolution or stabilization of the event (whichever occurs later).

Reasons for withdrawal of study treatment may include:

- Patient refused further treatment
- Pregnancy
- Unacceptable toxicity
- Significant study therapy non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

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 the 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 patient 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**.

Patients who meet the eligibility criteria and are randomized will have completed the following evaluations and assessments on Day 1 prior to treatment: review of any changes in medication history, physical examination, vital signs, clinical status – ordinal scale assessment and COVID-19-related symptoms scale assessment, EQ-D5-5L questionnaire, pulse oxygen saturation (SpO2), Nasopharyngeal Swab Sample Collection (for quantitative virologic testing viaRT-PCR), laboratory sample collection for routine serum biochemical, hematologic, coagulation, IL-6 levels and CRP, LDH, CPK, ferritin, D-dimer analysis.

During the treatment phase, patients randomized to the treatment arm A will receive CX-4945 (1000 mg) twice a day for up to 14 days. Details on CX-4945 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** Assessments in **Section 8.2.**

8.1.4. Unscheduled Visits

In the event that the patient 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 patient 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.

For samples being collected and shipped, detailed collection, processing, storage, shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.2.1. Safety Assessment

Safety assessments will include collection of adverse events (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 patient should have used 2 forms of contraception. Pregnancy tests will also be repeated at Day 14/EOT 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 (AEs)

Assessment of AEs will include the type, incidence, severity (as graded by a Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (https://www.fda.gov/media/73679/download)) 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. 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 AE.

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's 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,	For female patients of childbearing potential, serum or urine
Hematocrit	AST			
RBC	Alk Phos			
Platelets	LDH			

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

8.2.1.5. Electrocardiogram (ECG)

An ECG will be done at Screening and at Day 14/EOT. 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 patients to arrhythmias, 24-hour telemetry monitoring for patients with electrolyte abnormalities may be performed, if clinically indicated.

8.2.1.7. Pharmacokinetics Assessments

The PK of CX-4945 will be assessed using the data collected in two CX-4945 studies.

Note: PK samples have been collected from the first four patients by the time of release of Protocol Amendment 1. PK collection is not applicable for other patients.

Table 5. PK Sample Collection Times

Day	Time
Day 1	Pre-dose*
	30 minutes post morning dose ± 5 min.
	1 hour post morning dose ± 5 min
	2 hours post morning dose ± 5 min
	3 hours post morning dose ± 10 min
	6 hours post morning dose ± 10 min
Day 2	24 hours post Day 1 morning dose ± 60 min*
Day 14	Pre-dose*
	30 minutes post morning dose ± 5 min.
	1 hour post morning dose ± 5 min
	2 hours post morning dose ± 5 min
	3 hours post morning dose ± 10 min
	6 hours post morning dose ± 10 min
Day 15	24 hours post Day 14 morning dose ± 60 min
Day 16	48 hours post Day 14 morning dose ± 60 min
Day 17	72 hours post Day 14 morning dose ± 60 min

*On pre-dose sampling days, the CX-4945 morning dose must be administered in the clinic.

The following PK parameters will be calculated: Cmax, Tmax, AUC_{0-T}, AUC_{0-6}, and $T_{1/2}$.

8.2.2. Efficacy/Anti-viral Activity Assessment

8.2.2.1. COVID-19-Related Symptom Score Assessment

Clinical Symptom Score Assessment should be completed using a Patient Reported Outcome (PRO) instrument (a Patient Diary for Assessment of Common COVID-19-Related Symptoms – see Appendix 3). Each symptom is graded from 0 to 3, sense of taste/ smell is graded from 0 to 2 (see section 1.1 and section 3 for score values). Clinical Improvement will be assessed daily during the treatment phase from Day 1 through Day 14/EOT and on Day 28 and Day 45 of the Follow-up period.

If some abnormal symptoms are not related to COVID-19 and were caused by other conditions documented in medical history and started before COVID-19, the patient can be considered as recovered, when these symptoms return to the previous (pre-COVID-19) values.

8.2.2.2. Clinical Signs Evaluation to Assess Recovery

Assessment of recovery based on clinical signs includes normalization of fever, respiratory rate, heart rate 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 < 20 bpm while breathing room air with no shortness of breath
- SpO2 ≥ 96% in room air
- Heart rate <90 bpm

If some abnormal signs were caused by other conditions documented in the medical history and started before COVID-19, the patient can be considered as recovered, when these signs return to the previous (pre-COVID-19) values.

8.2.2.3. 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.

8.2.2.4. COVID-19 8-Point Clinical Progression Outcomes Scale

Progression is assessed on COVID-19 8-point outcomes scale at the time points described in the Schedule of Activities (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.

8.2.2.5. 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).

8.2.2.6. 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 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 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.

8.2.2.7. RT-PCR

RT-PCR (nasopharyngeal swab) will be done at the time points described in the Schedule of Activities (see Section 1.3). A positive RT-PCR test (presence of SARS-CoV-2 RNA) collected within 7 days prior to Day 1 is required at screening for patient eligibility evaluation. Local, fully validated, RT-PCR tests shall be performed at screening in a CLIA-certified and CAP-accredited laboratory.

8.3. ADVERSE EVENTS (AEs) AND SERIOUS ADVERSE EVENTS (SAEs)

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 AE

An 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 AE may or may not be related to the study treatment.

AEs will be elicited through direct questioning and patient reports. Any abnormality in physical examination findings or laboratory results that the investigator believes is clinically significant (CS) to the research patient 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 SAEs

A SAE is defined as any AE that:

- Results in death
- Is life threatening (the patient is at immediate risk of dying from the AE)
- Requires patient 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 SAE when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3. Classification of AEs

8.3.3.1. Severity of AE

As study population is outpatients with moderate COVID-19, a standardized toxicity grading scale is modified to reflect the study population. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials will be used for grading AEs associated with systemic (general) abnormalities, vital signs, illnesses and lab abnormalities. Full guidelines may be obtained at https://www.fda.gov/media/73679/download.

Table 6. Toxicity Grading General Guidelines

Grade	Description
Grade 1	Mild; No interference with activity
Grade 2	Moderate; Some interference with activity not requiring medical intervention
Grade 3	Prevents daily activity and requires medical intervention
Grade 4	Potentially Life-threatening ER visit or hospitalization
Grade 5	Death related to AE.

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 patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (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 patient's clinical state, environmental or toxic factors, or other therapies administered to the patient. (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 patient's clinical state, environmental or toxic factors, or other therapies administered to the patient. (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. **Unlikely 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 patient's clinical state, environmental or toxic factors, or other therapies administered to the patient. (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

The Medical Monitor will be responsible for determining whether an 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's Brochure.

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

8.3.4. Reporting of AEs

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

All AEs must be recorded in the patient'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 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 patient is no longer in the Treatment Phase of the protocol.

8.3.4.2. Treatment Given as a Result of the Event

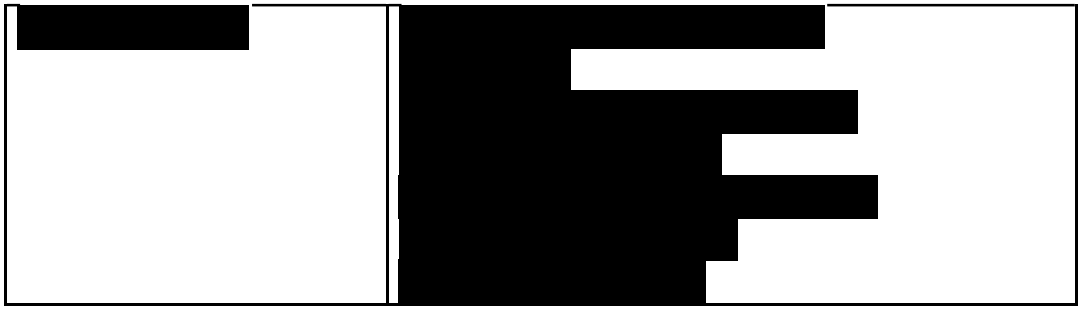
The event impact in terms of treatment provided will be as either: none, medication administered, non-drug therapy administered, hospitalization, or other (with a specification).

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 patient is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given patient, only the primary cause of death will have an outcome of death.

8.3.5. Reporting of SAEs

The Investigator is required to report all SAEs that occur during the time period specified in Section 8.3.4. Once the Investigator becomes aware of an SAE, he/she must report the SAE to Medical Monitor within 24 hours.



The Medical Monitor may request additional supporting documentation as it becomes available, such as lab reports, electrocardiogram [ECG] reports, discharge summary, hospital notes, etc., if applicable. Additional follow-up information as it becomes available must be reported to the Medical Monitor.

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 patients experiencing an SAE, including the discontinued patients, 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 patients 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 ARMS

There will be two treatment arms 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 1.1 and Section 3.

9.2.1. Safety Measures:

- Incidence and severity of AEs
- Incidence of 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 ECG results

9.3. SAMPLE SIZE DETERMINATION AND RATIONALE

A total of approximately 20 subjects will be randomized 1:1 in this study. The sample size is based on clinical judgment. No statistical power calculation is 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 group and SOC alone group to ensure balanced distribution of subjects. An individual, 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 patient data listings. Statistical analyses will be performed using SAS® for Windows, version 9.4 or later. 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 (ITT)Population

The **ITT population** is defined as all randomized patients. 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 (PP) Population

The PP population is defined as the set of patients 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 patient 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.

9.7.1.4. PK Population

The PK population includes all patients receiving at least one dose of CX-4945 and have adequate blood samples provided for PK evaluation and calculation of the PK parameters. PK data collected in two CX-4945 studies will be used for PK analysis.

9.7.2. Covariates

For efficacy analyses important prognostic factors that need adjustment will be specified in the 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 patients who have been randomized in the study to minimize missing data. However, in the event when there are missing data the following imputation methods will be used.

For efficacy evaluations, multiple imputation methods will be used to handle missing data and will be detailed in the SAP. This imputation method is a robust method to impute potential missing measurements. The imputation will be carried out in SAS version 9.4 or later using PROC MI.

9.8. ANALYSIS METHODS

An 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. Patient Disposition

The disposition of all patients 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-patient 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. All prior and concomitant medications recorded in the case report form 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. All concomitant medications/therapies recorded in the case report form will be listed.

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.

9.8.4.2. Supportive Analysis

To assess the consistency of the primary analysis results, supportive analysis will be conducted using the ITT and 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

AEs 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 SAEs, and AEs 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.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Patients will be identified on study records by a unique Patient 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 patient this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single patient.

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 patients 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 patient 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 patient 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 patient; or
2. When the modification does not involve the patient'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 patient for protocol violations. The IRB may also have to be contacted if safety to the patient 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 patient's rights, safety, or well-being 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 patient does not meet the protocol's eligibility criteria but was enrolled
- A research patient received the wrong treatment or incorrect dose.
- A research patient met withdrawal criteria during the study but was not withdrawn.
- A research patient received a prohibited concomitant medication.
- Failure to treat research patients 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 patient'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 patient'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 patient's participation in the trial or where it may be necessary to eliminate an immediate hazard to a research patient. 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 patients or when the modification does not involve the patient'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 to the study center participating in this study that cannot comply with these standards will be documented.

12.3. PATIENT INFORMED CONSENT REQUIREMENTS

All patients participating in this study will be given to by the Investigator and/or designee, written and oral information about the study in a language understandable by the patient. Written informed consent will be obtained from each patient prior any procedures or assessments that would not otherwise be required for the care of the patient are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the patient has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the patients 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 patient's study records, and a copy is provided to the patient. A second copy may be filed in the patient’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 patient'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 patients that will include each patient's study number, name, date of birth, and unique hospital identification number if applicable. A notation will be made in the patient'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 patients screened for participation in the study; it should include gender, age, eligibility status, reason for ineligibility, if applicable; and study allocated patient 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., patient's progress notes, AE 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
- Patient 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 Investigator/Sponsor and Senwha 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 Investigator/Sponsor and Senwha, shall not be disclosed to others without the written consent of Investigator/Sponsor and Senwha, 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 Investigator/Sponsor and Senwha. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities.

15. REFERENCES

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4. Rosenberger, A.F.N., Morrema, T.H.J., Gerritsen, W.H. et al. Increased occurrence of protein kinase CK2 in astrocytes in Alzheimer's disease pathology. J Neuroinflammation 13, 4 (2016). https://doi.org/10.1186/s12974-015-0470-x

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6. Koffa MD, Kean J, Zachos G, Rice SA, Clements JB. CK2 protein kinase is stimulated and redistributed by functional herpes simplex virus ICP27 protein. J Virol. 2003;77(7):4315-4325. doi:10.1128/jvi.77.7.4315-4325.2003

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 ❑

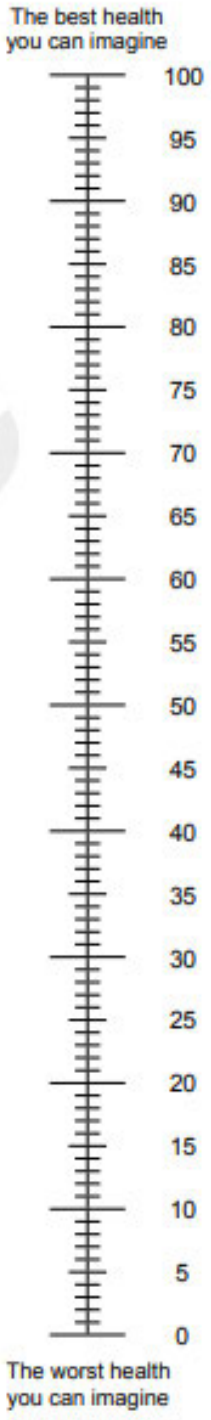
ANXIETY / DEPRESSION

- 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 ❑

2

- 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 = ☐



16.2. APPENDIX 2: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

For complete detailed information please refer to the link below:

https://www.fda.gov/media/73679/download

16.3. APPENDIX 3: ASSESSMENT OF COVID-19-RELATED SYMPTOMS (PATIENT DIARY)

Assessment of COVID-19-related symptoms

Subject Number: _____ Date and time of Assessment: _____

1. What was the severity of your **cough** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
2. What was the severity of your **sore throat** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
3. What was the severity of your **stuffy or runny nose** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
4. What was the severity of your **shortness of breath (difficulty breathing)** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
5. What was the severity of your **feeling of tightness of chest** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
6. What was the severity of your **feeling of fast heartbeat** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
7. What was the severity of your **low energy or tiredness** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
8. What was the severity of your **muscle cramps** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
9. What was the severity of your **joint pain** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
10. What was the severity of your **chills or shivering** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
11. What was the severity of your **feeling hot or feverish** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
12. What was the severity of your **difficulty in concentration (brain fog)** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
13. What was the severity of your **sleep disturbance (insomnia)** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
14. What was the severity of your **headache** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
15. What was the severity of your **dizziness** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
16. What was the severity of your **anxiety** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
17. What was the severity of your **feeling of tingling or numbness** in at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
18. What was the severity of your **nausea (feeling like you wanted to throw up)** at its worst over the last 24 hours? ☐ None ☐ Mild ☐ Moderate ☐ Severe
19. How many times did you **vomit (throw up)** in the last **24 hours**?* ☐ I did not vomit at all ☐ one or two times ☐ three or four times ☐ five or more times
20. How many times did you have **diarrhea (loose or watery stools)** in the last **24 hours**?* ☐ I did not have diarrhea at all ☐ one or two times ☐ three or four times ☐ five or more times
21. Rate your **sense of smell** in the last **24 hours** ☐ My sense of smell is THE SAME AS usual ☐ My sense of smell is LESS THAN usual ☐ I have NO sense of smell
22. Rate your **sense of taste** in the last **24 hours** ☐ My sense of taste is THE SAME AS usual ☐ My sense of taste is LESS THAN usual ☐ I have NO sense of taste

*The response options shown for items 19 and 20 are intended only for use with a 24-hour recall period.