A Dose Selection Phase 1 Study Evaluating the Safety and Tolerability of Silmitasertib (CX-4945) in Healthy Subjects

Protocol Number:	**CX4945-AV04-phase I**
Protocol version :	**1.0**
Date:	**30-August-2022**
Study Product:	**Silmitasertib (CX-4945)**
Sponsor:	**Senhwa Biosciences, Inc.** 10F, No. 225, Sec. 3, Peihsin Rd., Hsintien Dist., New Taipei City 23143, Taiwan Telephone: +886-2-8911-9856

PROTOCOL APPROVAL PAGE

Protocol Number:	**CX4945-AV04-phase I**
Protocol version:	**1.0**
Date:	**30-August-2022**

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

PROTOCOL APPROVAL FOR USE

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**CX4945-AV04-phase I**
Version :	**Version 1.0**
Date:	**30-August-2022**

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, Taiwan Food and Drug Administration (TFDA) 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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1. PROTOCOL SUMMARY

1.1. SYNOPSIS

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This is a Phase I single center, open-label, parallel design in 30 subjects to evaluate safety and tolerability of CX-4945 200mg QD, 200 mg BID and 400mg BID doses (10 subjects in each regimen) for continuously 5 days in healthy subjects for dose selection.

Prohibited Medications: Any drug contains ingredient of activated charcoal (such as Norit) are prohibited for 14 days during the study.</td></tr>
<tr><td>Primary Objective and Endpoints:</td><td><table><tr><th>Primary Objective</th><th>Primary Endpoint</th></tr><tr><td>To assess safety and tolerability of CX-4945 administered orally 200mg QD, 200mg BID and 400mg BID for continuously 5 days to healthy subjects</td><td>To evaluate the adverse events occurring from Day 1 to Day 5 (including vital signs, physical findings, clinical laboratory, and ECG results) as characterized by type, frequency, severity [as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 5.0], timing, seriousness, and relationship to study therapy after administration of 200mg QD, 200mg BID and 400mg BID for continuously 5 days to healthy subjects</td></tr></table></td></tr>
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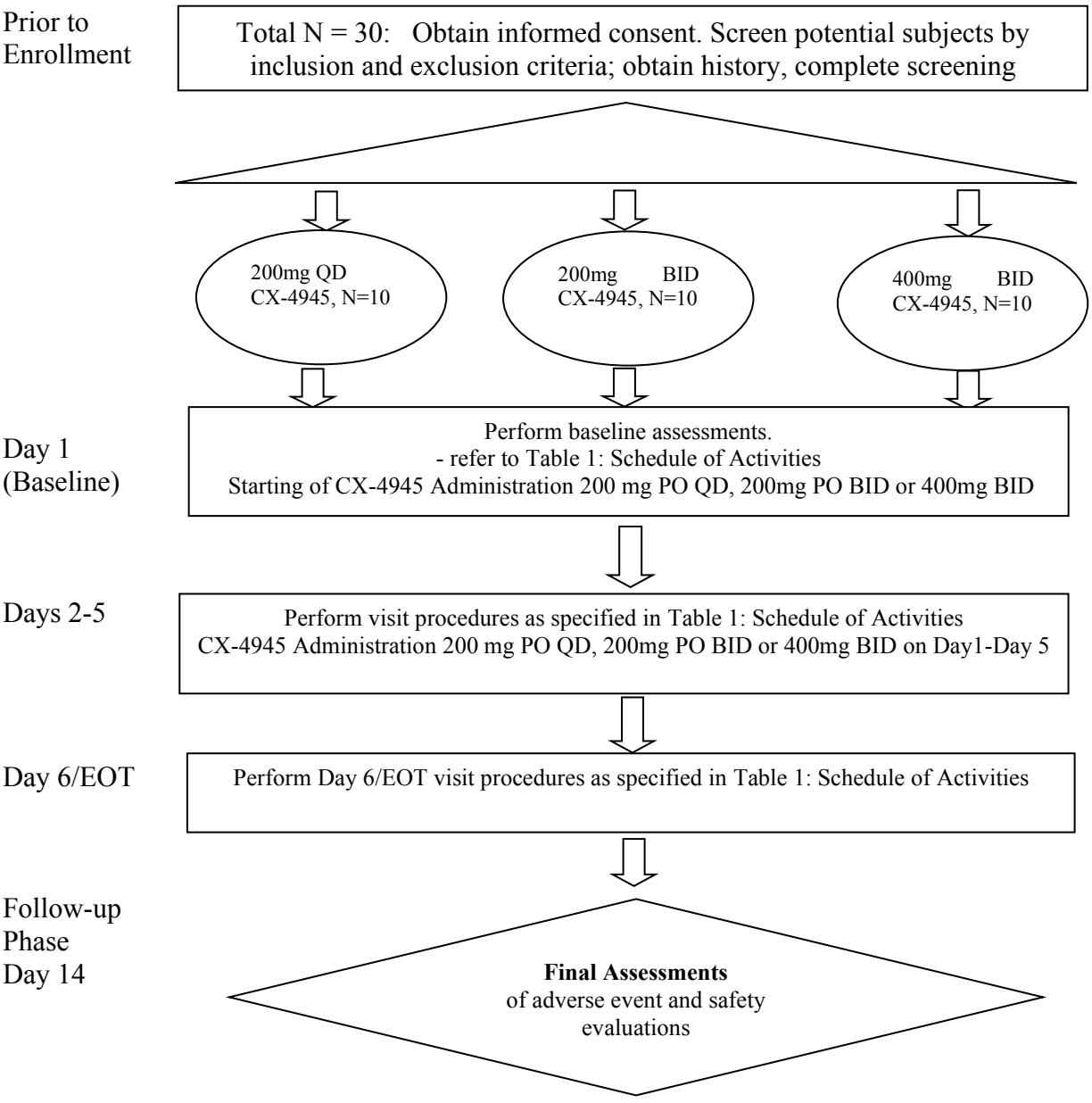
</table>

Study Population:	This study will enroll male and non-pregnant female ≥ 20 years of age with healthy subjects. Totally 30 subjects will be hospitalized and enrolled in this study.
Phase:	I
Description of Study Intervention:	CX-4945 will be administered at 200mg QD, 200mg BID or 400mg BID for continuously 5 days.
Study Duration:	5 months (from study initiation until completion of data analyses)
Subject Duration:	The total duration of the treatment will be 5 days. Subjects will be followed up at 14 days from the start of the treatment.

1.2. SCHEMA


Prior to Enrollment
Total N = 30: Obtain informed consent. Screen potential subjects by inclusion and exclusion criteria; obtain history, complete screening
200mg QD CX-4945, N=10
200mg BID CX-4945, N=10
400mg BID CX-4945, N=10
Day 1 (Baseline)
Perform baseline assessments.
- refer to Table 1: Schedule of Activities
Starting of CX-4945 Administration 200 mg PO QD, 200mg PO BID or 400mg BID
Days 2-5
Perform visit procedures as specified in Table 1: Schedule of Activities
CX-4945 Administration 200 mg PO QD, 200mg PO BID or 400mg BID on Day1-Day 5
Day 6/EOT
Perform Day 6/EOT visit procedures as specified in Table 1: Schedule of Activities
Follow-up Phase Day 14
Final Assessments
of adverse event and safety evaluations

1.3. SCHEDULE OF ACTIVITIES (SOA)

Table 1: Schedule of Activities

Procedure/Assessments	Screening Visit	Treatment				Follow-Up
Day	SV Day -28~ 0	Day 1 (Baseline)	Day 3	Day 5	Day 6 (EOT)	Day 14
Window Period		within 28 days after SV				±3 days
Informed Consent [1]	X					
Eligibility Evaluation [2]	X					
Subject Demographics	X					
Medical History [3]	X					
Physical Examination	X	X	X	X	X	X
Weight and Height	X					
Vital Signs [4]	X	X	X	X	X	X
ECG	X	X	X	X	X	
Laboratory Tests:	X	X	X	X	X	X
Hematology [5]	X	X	X	X	X	X
Blood Biochemistry [6]	X	X	X	X	X	X
Coagulation [7]	X	X	X	X	X	X
Serum/Urine Pregnancy Test [8]	X	X				X
Urinalysis [9]	X	X	X	X	X	X
Anti-HIV, Anti-HBV, Anti-HCV	X					
Anti-SARS-Cov2 [10]		X				
IP Administration		CX-4945 200 mg QD daily (Day 1 to Day5) CX-4945 200 mg BID daily (Day 1 to Day5) CX-4945 400 mg BID daily (Day 1 to Day5)				
Concomitant Medications	X	X	X	X	X	X

Adverse Events		X	X	X	X	X

[1] Informed consent must be obtained prior to subject participation in any protocol-related activities that are not part of routine care.

[2] Initial evaluation of subject eligibility will be performed by Investigator. Subject number will be assigned on Day1 after confirming the subject eligibility.

[3] Medical history and current therapies (medications and non-medications).

[4] Vital signs will include blood pressure, heart rate, respiration rate, SpO2, and temperature.

[5] Hematology: Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total, differential count,(Absolute Neutrophil Count, Absolute Lymphocytes Count, Absolute Monocytes Count, Absolute Eosinophils Count, Absolute Basophils Count) and platelets.

[6] Blood biochemistry:

- 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
- Electrolytes: sodium, potassium, chloride, magnesium, phosphorus, total calcium and bicarbonate,
- Other: Creatine phosphokinase (CPK), C-reactive protein (CRP), Creatine kinase-MB(CK-MB mass), Triglyceride, Total Cholesterol, Glucose AC, Uric Acid, γ-GT.

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

[8] ONLY performed on women of childbearing potential. Pregnancy Test will be tested on screening, Day 1 prior dosing and Day 14.

[9] 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.

[10] In response to the COVID-19 pandemic, the subject will need to follow the currently site's policies for COVID-19 to get the negative results of anti-SARS-Cov2 test before admission.

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 28 July 2022, more than 573 million cases have been confirmed, with more than 6.39 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.

[redacted]

Protein kinase, CK2, is a constitutively active serine/threonine kinase which has been studied as a pro-survival, anti-apoptotic kinase. Overexpression of CK2 has been reported in multiple cancers and shown to be linked to disease progression and poor prognosis. CK2 plays a crucial role in multiple non-oncogenic processes required to sustain the cancer phenotype, including the Hedgehog (Hh) pathway. Apart from oncology diseases, overexpression of CK2 has also been observed in some auto-immune and inflammatory diseases in vivo, and viral infections.

[redacted]

Understanding the safety and efficacy of CX-4945 will be the key of targeted COVID-19 therapies that can be used against the activated CK2 kinase signaling pathway in COVID-19.

2.2. CX-4945

[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]

[redacted]

2.3. OVERALL RISK AND BENEFIT ASSESSMENT

In the context of complications potentially associated with SARS-CoV-2 virus infection and the limitation of effective preventative measures in COVID-19 epidemics, the established pre-clinical toxicological profiles and mechanism of action of CX-4945 supports a favorable benefit/risk relationship of the product. This favorable relationship should translate into improved compliance

and offers an alternative program for mild to moderate COVID-19 treatment. It is hoped that the safety tolerability and the value of dose selection will be demonstrated in this healthy volunteer study, with sufficient safety data generated to enable dose selection for larger and more definitive Phase 2 studies.

3. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoint
To assess safety and tolerability of CX-4945 administered orally 200mg QD, 200mg BID and 400mg BID for continuously 5 days to healthy subjects	To evaluate the adverse events occurring from Day 1 to Day 5 (including vital signs, physical findings, clinical laboratory, and ECG results) as characterized by type, frequency, severity [as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 5.0], timing, seriousness, and relationship to study therapy after administration of 200mg QD, 200mg BID and 400mg BID for continuously 5 days to healthy subjects
Secondary Objectives	**Secondary Endpoints**
To evaluate changes in blood chemistry and other health assessment	Changes in blood chemistry and other health assessment from Day 1, Day 3, Day 5, and Day 6 morning.

4. STUDY DESIGN

4.1. OVERALL DESIGN

This is a phase I single center, open-label, parallel design in 30 subjects to evaluate safety and tolerability of CX-4945 200mg QD, 200 mg BID and 400mg BID doses (10 subjects in each regimen) for continuously 5 days in healthy subjects for dose selection. Up to approximately 30 subjects will be enrolled into this study. A screening evaluation will occur within 28 days prior to Day 1. A subject screening number will be assigned to each subject in successive order of consent signing, beginning with S001. At the end of screening all qualified subjects will be assigned sequentially to following three treatment cohorts:

- **Cohort 1:** CX-4945 200mg QD
- **Cohort 2:** CX-4945 200mg BID
- **Cohort 3:** CX-4945 400mg BID

A subject number will be assigned to participants when they have confirmed eligible for the study on Day1. Each cohort will receive a unique numeric designation, and will precede the subject number (e.g. at cohort 1 the first two subjects would be 01-001 and 01-002; at cohort 2 the first two subjects would be 02-001 and 02-002).

The total duration of the treatment will be 5 days. Subjects will be followed up at 14 days from the start of the treatment. The total duration for each subject in the study (including the screening) will be up to 42 days.

4.2. JUSTIFICATION FOR DOSE

[redacted]

4.3. STUDY STOPPING CRITERIA

During the study, serious adverse events will be reviewed by the sponsor as they are reported from the investigational center to identify safety concerns. The study may be terminated by the sponsor at any time.

At any time during the study and after discussion between the sponsor medical officer, medical monitor and investigator, the study may be stopped or terminated if the

following occur:

1. Previously unknown data that raise concern about the safety of the study participants become available

2. Three or more subject have experienced a clinical laboratory AE of Grade 3 or higher determined to be possibly or probably related to CX-4945.

4.4. END OF STUDY DEFINITION

A subject is considered to have completed the study if he or she has completed the Treatment Phase and Follow-up visits (Days 14).

Discontinuation from CX-4945 does not mean the withdrawal from the study assessments. Subjects who discontinued therapy should remain in the study and continue follow-up for key outcomes. The only reasons for end of study are withdrawal of consent and loss to follow-up,

5. STUDY POPULATION

This study will enroll up to approximately 30 healthy normal volunteers. All qualified subjects will be assigned sequentially to three treatment cohorts, CX-4945 200mg QD, 200 mg BID and 400mg BID doses and be hospitalized for 6 days treatment.

5.1. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects 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 subject is suitable for this protocol.

5.1.1. Inclusion Criteria

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

1. Healthy male and female subjects 20 to 55 years of age, inclusive, at screening
2. Body mass index (BMI) within the range of 18.0 to 30.0 kg/m^2, inclusive, and a minimum weight of 50.0 kg at screening
3. Subjects who are of reproductive potential agreed to remain abstinent or use (or have their partner use) an acceptable method of birth control (intrauterine device, hormonal contraception, vasectomy or condom) from screening until at least 2 weeks after the last study drug administration.
4. Physically and mentally healthy subjects as confirmed by an interview, medical history, clinical examination, and electrocardiogram;
5. Subject with acceptable hematology, biochemistry and urinalysis during screening period.
6. Subject is willing and able to comply with study procedures and sign informed consent.

5.1.2. Exclusion Criteria

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

1. 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 from screening until at least 2 weeks after the last study drug administration. 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.

2. Active or uncontrolled infections such as COVID-19, HIV or with serious illnesses or medical conditions which would not permit the subject to receive study treatment.
3. Subject has received any prescription of drug within 3 days prior to study enrollment.
4. Subject has drug abuse history.
5. Any active or recurring clinically significant hepatic disease including HBV and HCV.
6. Subject has received any investigational agent within 28 days or 5 half-lives, whichever is longer, prior to the first dose of investigational product.
7. Any other medical reason as determined by the investigator.

5.2. SCREEN FAILURES

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

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

5.3. SUBJECT REPLACEMENT

All subjects who are removed from the study for any reason other than for adverse events (e.g., voluntary discontinuation at the subjects request, or a severe violation of the study protocol) will be replaced. Data from these removed subjects will be included in the overall safety analysis. If subject completed the treatment (Day1 to Day5) but not finished the Day 14 follow up visit, the subject will not be replaced.

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 three cohorts.

Refer to the Investigator's Brochure for more information.

6.1.2. Dosing and Administration of CX-4945

Subject enrolled to the treatment cohort 1 will receive 200 mg of CX-4945 QD by mouth, beginning on Day 1, and continuously through Day 5. The cohort 2 and cohort 3 will receive 200 mg and 400mg of CX-4945 BID by mouth, beginning on Day 1, and continuously through Day 5.

Other oral medications should be taken at least one hour before or 2 hours after ingesting the dose of CX-4945 capsules.

Subjects will take 1-2 200-mg CX-4945 capsules, two hours after the morning meal and two hours after the evening meal (dinner) with water. Subjects 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 subject can take as much as 10 minutes to swallow 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 subject will be NPO (except for water) for 2 hours, after which, the subject may eat.

Subject will take 3 meals a day provided by hospital. If any reason to have an extra food should be approved by investigator. Subjects are not allowed to smoke during the 5 days treatment.

6.1.3. CX-4945 Compliance

Site staff will dispense CX-4945 to the subjects assigned to the cohort 1, 2 or 3. The site staff will make sure that the subject will take the IP properly. Any missed doses or non compliance should be documented in the dosing record form. The IP will be counted, documented, and recorded by site staff.

6.1.4. CX-4945 Dose Discontinuation

The most common drug related adverse events reported for CX-4945 are predominantly gastrointestinal disorders, including nausea, vomiting and diarrhea. Treatment with CX-4945 can be discontinued prematurely due to the following reasons:

- Subject have experienced a clinical laboratory AE of Grade 2 or higher determined to be possibly or probably related to CX-4945
- Withdrawal from the study treatment or participation
- Pregnancy
- Lost to follow-up
- Reported major protocol deviations, as determined by the Investigator or the Sponsor
- Subject is treated with or takes a prohibited medication.
- 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 subject.

Discontinuation from CX-4945 does not mean the withdrawal from the study assessments. Subjects who discontinued therapy should remain in the study and continue follow-up for key outcomes. The only reasons for end of study 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 subject. The clinical site pharmacy /qualified staff member will dispense the supplies to the subject enrolled to the cohort 1 to 3 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]

[redacted]

6.3. CONCOMITANT MEDICATION

Investigators should always manage their subjects according to their medical judgement based on the particular clinical circumstances. Any drug contain ingredient of activated charcoal (such as Norit) are prohibited for 14 days during the study.

[redacted]

[redacted]

7. STUDY COMPLETION OR DISCONTINUATION

7.1. SUBJECT COMPLETION

A subject is considered to have completed the study if he or she has completed the treatment phase and Follow-up visits at Day 14.

Discontinuation from CX-4945 does not mean the withdrawal from the study assessments. Subjects who discontinued therapy should remain in the study and continue follow-up for key outcomes. The only reasons for end of study are withdrawal of consent from further participation in the study and loss to follow-up.

7.2. SUBJECT WITHDRAWAL FROM PARTICIPATION IN THE STUDY

At any point during the study all subjects 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 subject refuses further visits, the subject should continue to be followed unless the subject 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. SUBJECT DISCONTINUATION FROM STUDY TREATMENT

Subjects 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 subject to comply with the protocol-required schedule of study visits or procedures at a given investigator site.
All subjects who discontinued from study treatment but maintain consent, should remain in the study through the end of the study period for all important safety assessments.

Investigators considering subject withdrawal from study treatment should contact the medical monitor prior to such discontinuation. Subjects 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 subjects.

Subjects 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:

- Subject refused further
- 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
- 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.**

8.1. STUDY PROCEDURES

8.1.1. Screening Period:

The subject will sign and date the informed consent form (ICF) prior to any study-related procedures. The study center will maintain the study-specific screening and enrollment logs at their site.

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

8.1.2. Treatment Period:

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

Subjects who fulfill all the entry criteria and have written informed consent will be enrolled to the study. Enrollment is specifically referred to the visit of treatment on Day 1. All subjects will be 5-days hospitalized during treatment period. Clinical visit will be scheduled to occur at the intervals indicated as Table 1. After confirming satisfaction of check-in procedure, the subjects will be assigned a subject number and 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 –laboratory sample collection for routine serum biochemical, hematologic, coagulation analysis.

Eligible subjects will be assigned to one of cohort groups to receive the study drug. Considering a ~15% screen failure rate, approximately 45 subjects will be screened in order to recruit 30 evaluable subjects.

During the treatment phase, subjects assigned to the cohort 1 will receive CX-4945 (200 mg) once a day for up to 5 days. For cohort 2, subjects will receive CX-4945 (200 mg) twice a day for up to 5 days. For cohort 3, subjects will receive CX-4945 (400 mg) twice a day for up to 5 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 subject will return to clinic at a time other than a regularly scheduled study visit, the visit will be regarded as an unscheduled visit. Assessments at unscheduled visits are at the discretion of the Investigator. All pertinent findings, including adverse events or changes in medications, will be noted in the subject medical records.

8.2. ASSESSMENTS

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

8.2.1. Safety Assessment

Safety assessments will include collection of 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. For female subjects of childbearing potential, a negative pregnancy test is required before receiving CX-4945 (1 negative pregnancy test at screening and 1 negative pregnancy test at day1 prior CX-4945 dosing). Following a negative pregnancy test result at screening, appropriate contraception must be commenced. For women of childbearing potential subject should have used hormonal or barrier method of birth control; or abstinence as highly effective contraception from screening until at least 2 weeks after the last study drug administration.

Subjects who are found to be pregnant during the screening period will be a screen failure. Subjects who are found to be pregnant during the treatment period will be asked to discontinue study treatment.

8.2.1.2. Adverse Events (AEs)

Assessment of AEs will include the type, incidence, severity (graded by the CTCAE version 5.0) timing, seriousness, and relatedness. For AE assessment details, see **Section 8.3.3.** Investigator will follow-up for any AEs/SAEs at Day 14.

8.2.1.3. Vital Signs and Physical Examination

Subjects will have a full physical examination to include an examination of all major body systems, height (at screening only), weight (at screening only), blood pressure, respiration rate, SpO2, temperature and heart rate, which may be performed by a physician, registered nurse or other qualified health care provider, as acceptable according to local regulation. The physical examination, assessing the subject's overall health and physical condition, will be performed according to the site's SOPs. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded but only clinically significant abnormalities will 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.

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 2. Safety Laboratory Tests

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

Hematology	Biochemistry	Coagulation	Urinalysis	Pregnancy Test
Absolute Lymphocytes	Potassium		microscopic examination of urine sediment	
Absolute Monocytes	BUN			
Absolute Eosinophils	Chloride			
Absolute Basophils	Total Calcium			
	Magnesium		**Serology**	
	Phosphorus		Anti-HIV	
	Bicarbonate		Anti-HCV	
	Total bilirubin		Anti-HBV	
	Creatinine (serum)			
	Albumin		**Others**	
	C-reactive protein (CRP)		Anti-SARS-Cov2	
	Creatine Phosphokinase (CPK)			
	Creatine kinase-MB(CK-MB mass)			
	Triglyceride			
	Total Cholesterol			
	Glucose AC			
	Uric Acid			
	γ-GT			

8.2.1.5. Electrocardiogram (ECG)

An ECG will be done at Screening, Day 1, Day 3, Day 5, and at Day 6. 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.

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

8.3.2. Definition of SAEs

A SAE is defined as any AE that:

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

8.3.3. Classification of AEs

8.3.3.1. Severity of AE

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

Table 3. CTCAE v5.0 General Guidelines

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

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

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

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

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

8.3.3.2. Causality Assessment

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

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

with certainty to the study treatment. An AE may be considered possible if or when (must have two): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.

4. **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 subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It does not follow a known response pattern to treatment with the study treatment.
5. **Unrelated**: This category applies to those AEs which, after careful consideration at the time they are evaluated, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and determined with certainty to have no relationship to the study treatment.

8.3.3.3. Expectedness

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 subject completes the study. A final assessment of outcome will be made at that time.

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

8.3.4.1. Impact on Study Treatment

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

8.3.4.2. Treatment Given as a Result of the Event

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

8.3.4.3. Outcome Assessment

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

8.3.5. Reporting of 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 Sponsor's Contract Research Organization (CRO) Safety Department within 24 hours.

Safety Department	[redacted]

The designee in Safety Department 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 designee in Safety Department.

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

8.3.6. SAE Follow-Up

All subjects experiencing an SAE, including the discontinued subjects, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event

stabilizes at a level acceptable to the investigator (i.e., recovery, return to baseline status, no further improvement expected, or death).

For each SAE indicated as an unresolved event on the initial report, regardless of whether the subjects 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 COHORTS

There will be three cohorts in the study:

- Cohort 1: CX-4945 200mg QD
- Cohort 2: CX-4945 200mg BID
- Cohort 3: CX-4945 400mg BID

The total duration of the treatment will be 5 days. Subjects will be followed up at 14 days from the start of the treatment.

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, heart rate, respiratory rate, SpO2, systolic and diastolic blood pressure, urinalysis
- Changes in physical examination results
- Changes in ECG results

9.3. SAMPLE SIZE DETERMINATION AND RATIONALE

A total of 30 subjects will be assigned sequentially into 3 cohorts 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. BLINDING

This is an open label study.

9.5. INTERIM ANALYSIS

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

9.6. GENERAL STATISTICAL CONSIDERATIONS

All collected study data will be presented in subject 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.

9.6.1. Analysis Populations

9.6.1.1. Intent-to-Treat (ITT)Population

The ITT population is defined as all assigned subjects who received at least one dose of study drug. This population will be used as the primary analysis population for analysis of the primary and secondary endpoints.

9.6.1.2. Per Protocol (PP) Population

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

9.6.1.3. Safety Population

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

9.6.2. Missing Data

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

9.7. 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.

9.7.1. Subject Disposition

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

9.7.2. 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.

9.7.3. 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.

9.7.4. 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.

9.7.4.1. 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.

9.7.4.2. 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. DATA MONITORING COMMITTEE (DMC)

Throughout the trial, all safety and tolerability data will be reviewed and monitored by an independent DMC. The composition and functions of the DMC will be governed by a charter, which will be described elsewhere.

At a minimum, safety data include all observations generated as part of study procedures and SoC that have been captured in the CRF. At the discretion of the DMC, this may be extended to include all relevant source records and, potentially, portions of the medical record of clinical care that have not been captured in source records.

The DMC will consist of at least 3 key opinion leaders, of which 1 will serve as the Chairperson. Due to the small sample size, a Statistician will not form part of the DMC. Data obtained from the all subject will be reviewed by the DMC.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

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

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

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. MONITORING REQUIREMENTS

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

12.2. MODIFICATION OF PROTOCOL

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

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

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

12.3. REPORTING PROTOCOL DEVIATIONS

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

12.3.1. Major Protocol Deviation or Violation

A major protocol deviation or violation is a deviation from the IRB approved protocol that may affect the subject 's rights, safety, or 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 subject does not meet the protocol's eligibility criteria but was enrolled
- A research subject received the wrong treatment or incorrect dose.
- A research subject met withdrawal criteria during the study but was not withdrawn.
- A research subject received a prohibited concomitant medication.
- Failure to treat research subject 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.

12.3.2. Minor Protocol Deviation or Violation

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

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

13. ETHICS AND REGULATORY REQUIREMENTS

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

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

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

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

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

13.2. 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.

13.3. SUBJECT INFORMED CONSENT REQUIREMENTS

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

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

14. DATA HANDLING AND RECORD KEEPING

14.1. RECORDING AND COLLECTION OF DATA

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

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

14.2. ARCHIVING

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

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

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

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

Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., subject's progress notes, 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
- Subject screening
- SAE reports
- IRB approval and re-approval letters
- Completed quality of life questionnaire
- Other documents pertaining to the conduct of the study

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

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

15. PUBLICATION PLAN

All information supplied by 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 Senwha, shall not be disclosed to others without the written consent of Senwha, and shall not be used except in the performance of this study.

16. REFERENCES

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