CLINICAL STUDY PROTOCOL

Evaluation of the Safety and Efficacy of Silmitasertib (CX-4945) in Combination with Standard of Care (SOC) for Treating Patients with Community-Acquired Pneumonia (CAP) Associated with SARS-CoV-2 and Influenza Viral Infections

Protocol Number:	CX-4945-011
Investigational Product:	Silmitasertib (CX-4945)
Phase:	2
Sponsor:	Senhwa Biosciences, Inc. 10F, No. 225, Sec. 3, Peihsin Rd., Hsintien Dist., New Taipei City 23143, Taiwan
Protocol Date:	16 August, 2024
Protocol Version:	3.0

SIGNATURE PAGE

Study Title:

Evaluation of the Safety and Efficacy of Silmitasertib (CX-4945) in Combination with Standard of Care (SOC) for Treating Patients with Community-Acquired Pneumonia (CAP) Associated with SARS-CoV-2 and Influenza Viral Infections

Objective:

Clinical Study Protocol

I have read the protocol and agree to conduct this clinical study in accordance with all stipulations of the protocol, with applicable law and regulations and in accordance with the ethical principles outlined in the Declaration of Helsinki.

SPONSOR:

Senhwa Biosciences, Inc. **Date**

PROTOCOL ACKNOWLEDGEMENT FORM

SPONSOR:

Senhwa Biosciences, Inc.

CLINICAL PROTOCOL RECEIPT

PROTOCOL NUMBER:

CX-4945-011

PROTOCOL TITLE:

Evaluation of the Safety and Efficacy of Silmitasertib (CX-4945) in Combination with Standard of Care (SOC) for Treating Patients with Community-Acquired Pneumonia (CAP) Associated with SARS-CoV-2 and Influenza Viral Infections

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I have received and read the Clinical (Amendment) Protocol for the above noted trial. I have agreed to conduct this clinical study in accordance with all stipulations of the protocol, with applicable law and regulations and in accordance with the ethical principles outlined in the Declaration of Helsinki

Principal Investigator (PI) Name (print): _____

Site Number: _____

Site Name: _____

PI Signature: _____ Date: _____

SYNOPSIS

<table>
<tr><td>Title:</td><td>Evaluation of the Safety and Efficacy of Silmitasertib (CX-4945) in Combination with Standard of Care (SOC) for Treating Patients with Community-Acquired Pneumonia (CAP) Associated with SARS-CoV-2 and Influenza Viral Infections</td></tr>
<tr><td>Phase:</td><td>Phase 2</td></tr>
<tr><td>Site Locations:</td><td>The study will be conducted in multiple centers in Taiwan.</td></tr>
<tr><td>Study Description and Design:</td><td>This is a Phase II, multi-center, double-blind, randomized, interventional study in approximately 120 subjects to evaluate clinical benefit of CX-4945 in adult outpatients with SARS-CoV-2 and influenza viral infection-associated pneumonia. The subjects will be recruited into two domains, including SARS-CoV-2 and influenza virus domains. The study will compare the efficacy of Standard of Care (SOC) combined with CX-4945 against SOC paired with a placebo, utilizing a 1:1 allocation ratio in each domain. The study arms will be listed below:

Domain I: SARS-CoV-2 domain

Arm 1: CX-4945 (400 mg BID for 5 days) + SOC

Arm 2: Placebo + SOC

Domain II: Influenza virus domain

Arm 3: CX-4945 (400 mg BID for 5 days) + SOC

Arm 4: Placebo + SOC

Screening visit will collect health information and perform protocol-specified tests to determine patients' eligibility. After screening visit, eligible subjects who fulfill all selection criteria for enrollment will be randomized into each of the arms. The CX-4945 will be administered at 400 mg BID for 5 days. Subjects will be followed up until Day 29.

Subjects will return to clinics site for 5 designated visits: Visit 1 (Day -2 ~ 1, screening), Visit 2 (Day 1, baseline, randomization, the start of treatment), Visit 3 (Day 7 ± 1, the end of treatment), Visit 4 (Day 15 ± 2, 1st follow-up), and Visit 5 (Day 29 ± 3, 2nd follow-up, the end of study). The hospitalization and emergency visit due to CAP related to SARS-CoV-2 or influenza infection, chest X-ray, body temperature, pulse oxygen saturation for SpO_2/FiO_2 ratio will be monitored. RT-PCR will be performed to assess the reduction of viral presence and to measure viral load (SARS-CoV-2 only). Safety issues, including 12-lead ECG, laboratory tests, vital signs, and adverse events will be evaluated after treatments during study period.</td></tr>
<tr><td>Purpose:</td><td>The purpose of this trial is to investigate whether intervention with Silmitasertib (CX-4945) prevents the progression of CAP and moderates the elevated cytokine release associated with SARS-CoV-2 and influenza virus infection.</td></tr>
<tr><td>Primary Objective and Endpoints:</td><td>
<table>
<tr><th>Primary Objective</th><th>Primary Endpoint</th></tr>
<tr><td>To evaluate the effect of intervention with</td><td>• The percentage of subjects requiring hospitalization, emergency room visits,</td></tr>
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</td></tr>
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	Silmitasertib (CX-4945) in addition to SOC, compared to placebo plus SOC, in preventing the progression of CAP associated with SARS-CoV-2 and influenza virus infection	or resulting in death due to progression of CAP related to SARS-CoV-2 or influenza. (Time Frame: Day 1 to Day 29)
Secondary Objectives and Endpoints:	**Secondary Objectives**	**Secondary Endpoints**
	To evaluate the effect of intervention with Silmitasertib (CX-4945) in addition to SOC, compared with placebo plus SOC, in enhancing the subject's clinical condition	• The percentage of subjects with all cause hospitalization, emergency room visits, or death during study period (Time Frame: Day 1 to Day 29) • The percentage of subjects with improved pulmonary X-ray findings for pneumonia, relative to baseline or showing a return to normalcy (Time Frame: Baseline to Day 7, 15, and 29) • Time to symptom resolution for fever The symptom resolution for fever is defined as body temperature lower than the following definition for 24 hours (ear temperature < 38 °C, base of the tongue temperature < 37.5 °C, or axillary temperature < 37 °C) • Change from baseline in SpO_2/FiO_2 ratio (Time Frame: Day 1 to Day 7, 15, and 29) • The percentage of subjects exhibiting disease progression in health status Disease progression is defined as an increase of score on the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale (Time Frame: Day 1 to Day 7, 15, and 29) • The percentage of subjects exhibiting health improvement in health status Health improvement is defined as a reduction of score on the NIAID 8-point ordinal scale. (Time Frame: Day 1 to Day 7, 15, and 29)
	To evaluate the effect of intervention with Silmitasertib (CX-4945) in addition to SOC, compared with placebo	• The percentage of subjects with a negative RT-PCR result for the SARS-CoV-2 (only for SARS-CoV-2 domain) or the influenza virus (only for influenza virus domain) on

	plus SOC, on reducing viral presence	Day 7 FilmArray data (Negative/Positive) obtained from Protocol v.1.0 will be integrated into and considered equivalent to the results for RT-PCR. (Time Frame: Day 1 to Day 7) • Change from baseline in viral load in nasal secretions by RT-PCR (only for SARS-CoV-2 domain) (Time Frame: Day 1 to Day 7) • Change from baseline in Ct values (only for SARS-CoV-2 domain) (Time Frame: Day 1 to Day 7)
	To evaluate the safety and tolerability of Silmitasertib (CX-4945)	• TEAEs and SAEs (Time Frame: Day 1 to Day 29) • Laboratory test (Time Frame: Day 1 to Day 29) • Vital signs (Time Frame: Day 1 to Day 29) • Electrocardiogram (ECG) results (Time Frame: Baseline to Day 29)
Exploratory Objectives and Endpoints:	**Exploratory Objectives**	**Exploratory Endpoints**
	To evaluate the effect of intervention with Silmitasertib (CX-4945) in addition to SOC, compared with placebo plus SOC, on inflammatory status	• The percentage of subjects achieving normalized [redacted] levels on Day 7 This statistical analysis will only be conducted in subjects [redacted] levels exceed the upper limit of normal (ULN) at Visit 2. (Time Frame: Day 7) • Change from baseline in [redacted] (Time Frame: Day 1 to Day 7, 15, and 29) *Note: If the flow cytometry analyses [redacted] are not performed at the local site lab, the related endpoint can be omitted.*
	To evaluate the effect of intervention with Silmitasertib (CX-4945)	[redacted] Changes from baseline in serum cytokine levels: [redacted]

	in addition to SOC, compared with placebo plus SOC, on moderating the elevated cytokine release associated with SARS-CoV-2 and influenza virus infection	[redacted] (Time Frame: Day 1 to Day 7, 15, and 29)
Participant Group/Arm:	**Domain I: SARS-CoV-2 domain** Arm 1: CX-4945 (400 mg BID for 5 days) + SOC Arm 2: Placebo + SOC Note: The SOC within the SARS-CoV-2 domain is defined as the medications in use at each respective site for the treatment of CAP related to SARS-CoV-2 infection. **Domain II: Influenza virus domain** Arm 3: CX-4945 (400 mg BID for 5 days) + SOC Arm 4: Placebo + SOC Note: The SOC within the influenza virus domain is defined as the medications in use at each respective site for the treatment of CAP related to influenza virus infection.	
Study Duration:	The study duration for each subject is up to 34 days, including screening, a treatment period of 5 days and a follow-up phase lasting until Day 29.	
Eligibility Criteria:	**Inclusion Criteria** 1. Not currently hospitalized 2. Males or females aged ≥ 18 years at the time of signing the informed consent form (ICF) 3. Patients diagnosed with viral pneumonia, as determined by the investigator, who exhibit any of the subsequent criteria: presence of respiratory symptoms or fever (ear temperature ≥ 38 °C, base of the tongue temperature ≥ 37.5 °C, or axillary temperature ≥ 37 °C) 4. With a pneumonia severity index (PSI) of risk class II or III 5. Oxygen saturation measured by pulse oximetry (SpO_2) ≥ 94% on room air at sea level 6. Positive test for SARS-CoV-2 or influenza virus infection, confirmed by rapid diagnostic test (excluding cases where both SARS-CoV-2 and influenza virus are positive) 7. Confirmed lower respiratory tract infection by X-ray 8. At screening, subjects capable of childbearing must provide a negative serum or urine pregnancy test. These subjects must also commit to adhering to the study-specified contraceptive methods throughout the study duration **Notes:** Acceptable contraceptive methods include:	

- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps)

9. The participant (or legal representative) agrees and is able to adhere to study protocol-stated requirements, instructions, and restrictions in the investigator's judgement. Furthermore, the participant is capable of understanding and has signed the IRB-approved Informed Consent Form (ICF)
10. With at least two of the risk factors listed below:

    Age ≥ 50 years-old; cancer and a life expectancy of ≥ 6 months; HIV infection; immunocompromised patient; congestive heart failure (CHF), or coronary artery disease (CAD), or cardiomyopathies; chronic kidney disease (CKD); chronic liver disease; chronic lung disease; diabetes mellitus (DM); body mass index (BMI) > 25 kg/m^2; asthma; cerebrovascular disease; cystic fibrosis; dementia; or current and former smoker

Exclusion Criteria

1. Subject received investigational treatment within 30 days prior to the study, or concurrent use of another investigational drug
2. Subject has a history of severe renal disease (required phosphate binders or dialysis)
3. Subject has chronic diarrhea, characterized by three or more loose stools daily for a minimum of four weeks
4. High likelihood of mortality within the next 48 hours, as assessed by the investigator
5. Subject showing signs of respiratory failure and mechanical ventilation is required
6. Subject with liver cirrhosis
7. Subject with hepatitis B and/or hepatitis C disease, unless the subject has an aspartate aminotransferase (AST) level ranging from 8 to 31 U/L and an alanine aminotransferase (ALT) level from 0 to 41 U/L
8. Known active tuberculosis
9. Current documented bacterial infection
10. Subject has a documented anaphylactic reaction, regardless of cause
11. Subject who has taken an antiviral agent against respiratory viral infection for a continuous duration of more than 24 hours before screening
12. Subject is with active gastrointestinal diseases including gastritis,

	ulcerative colitis, Crohn's disease, or hemorrhagic coloproctitis 13. Subjects received warfarin within 14 days prior to screening or intend to during the screening or treatment phase 14. History of allergic reactions to any of the ingredients or components used in the manufacture of CX-4945 15. Women who are pregnant or breastfeeding, or planning pregnancy during the study **Note:** Men and women of reproductive potential must commit to effective contraception methods or abstinence during the study. Any resulting pregnancies or suspected pregnancies must be reported to the treating physician immediately. 16. ALT or AST levels > 5 times upper limit of normal (ULN) 17. eGFR <30 mL/min/1.73m^2 (calculated by the MDRD formula) 18. Absolute neutrophil count (ANC) <1000/μL 19. Have received treatment with a SARS-CoV-2 specific monoclonal antibody 20. Have received convalescent COVID-19 plasma treatment 21. Concurrent use of baricitinib 22. Any physical findings or illness history that may compromise study results or increase patient risk, as determined by the investigator
Treatment Regime and Duration	CX-4945 will be administered at 400 mg BID for 5 consecutive days starting on Day 1 in addition to SOC.
Sample Size Determination	To ensure 120 evaluable participants (= modified Per-Protocol population) and accounting for a 10% attrition rate, approximately 136 subjects will be enrolled for the study. Note that the sample size for this exploratory study is not determined by statistical power considerations, but is considered adequate for the preliminary assessment of the study's objectives. To have an adequate efficacy profile of the intervention with CX-4945 in SARS-CoV-2 and influenza virus infection, the minimum evaluable size per arm in each study domain will be 20 participants.
Statistics	1. Primary hypothesis: Not applicable. 2. Efficacy population: ■ITT ■ PP ■Other: mPP Safety population: ■ITT ■PP □Other: The Intent-to-Treat (ITT) population is defined as all randomized subjects who receive at least one dose of CX-4945 or placebo. This population will be used as the primary analysis population for efficacy endpoints and safety evaluation. The Per-Protocol (PP) population is defined as the set of subjects who (1) meet the ITT population requirements, (2) receive 80 – 120% of 10 doses of investigational product during Days 1 – 6 or die before Day 6, and (3) are not associated with any major protocol violations that have impact on

efficacy evaluation. This population will be identified before the database lock. This population will be used as the supportive analysis population for efficacy endpoints and adverse events.

The modified Per-Protocol (mPP) population is defined as the set of subjects who (1) meet the ITT population requirements, (2) receive 80 – 120% of 10 doses of investigational product during Days 1 – 6 or die before Day 6, (3) complete the required visits by Visit 4 or die before Visit 4, and (4) are not associated with any major protocol violations that have impact on efficacy evaluation by Visit 4. This population will be identified before the database lock and will be used as the supportive analysis population for efficacy endpoints.

3. Statistical method(s) for efficacy/safety evaluations

General Consideration

Statistical analyses will be performed using SAS® for Windows, version 9.4 or later. All available data will be displayed via subject data listings, and summarized for each evaluation time point as appropriate by study domain (including domain-pooled) and study arm. The categorical data will be summarized with the number of subjects and percentage. Continuous data will be summarized by descriptive statistics (i.e., number of subjects, mean, standard deviation, minimum, maximum, and median). For by visit (by Day) analyses, the acceptable window for each visit will be defined in the Statistical Analysis Plan (SAP).

In general, categorical data will be analyzed by using Logistic regression (on efficacy data), Fisher's exact test or Cochran-Mantel-Haenszel test stratified by domain for comparing overall treatment group difference (treatment odds ratio for Logistic regression). For by-domain subgroup analysis on efficacy data, categorical data will be tested by using Fisher's exact test or Chi-square test.

Continuous data will be analyzed by using analysis of variance (ANOVA) on baseline data, and by using analysis of covariance (ANCOVA) on change data for comparing overall treatment group difference. Non-parametric method shall be adapted or log-transformation may be needed for non-normally distributed data. For by-domain subgroup analysis on efficacy data, continuous data will be tested by using two-sample t test or Wilcoxon Rank-sum test.

For the ANOVA, ANCOVA model and Logistic regression, factors of treatment, domain (as appropriate), site and baseline value (for post-baseline data) and other baseline factors (for post-baseline efficacy data, to be defined in the SAP, as appropriate) will be included in the model if significant, those non-statistically significant factors except treatment will be removed from the model (alpha=0.1 for interaction, 0.05 for others). The Logistic regression result will be presented with treatment odds ratio and its 95% confidence interval (CI).

All statistical tests will be two-sided and evaluated at the 0.05 level of significance. All confidence intervals, if provided, will be the 95% CI.

The most recent value before first dose administration will be defined as the baseline value; therefore, the baseline value will be the outcome of the

	closest evaluation performed before or equal to the first dosing date. **Efficacy evaluation** The primary efficacy endpoint is the percentage of subjects with the event of requiring hospitalization, emergency room visits, or resulting in death due to progression of CAP related to SARS-CoV-2 or influenza. For subjects terminated the study that event observation stopped before Day 29 and no event is observed, the subjects will be counted as 'Treatment Fail'. The primary endpoint will be summarized in number of subjects and percentage with corresponding Clopper-Pearson exact 95% CI, and will be analyzed by using Logistic regression. Fisher's exact test or Cochran-Mantel-Haenszel test will be applied if Logistic regression is not applicable. In addition, 95% CI of treatment difference in event rate will be presented in normal approximation. Event rate including Treatment Fail rate will be tested additionally for sensitivity analysis defined in SAP. **Safety Evaluation** All safety assessments, including TEAEs, physical examination, laboratory tests, vital signs, and electrocardiogram results, where indicated, will be presented using descriptive statistics. 4. Planned interim analysis: ☐Yes ■No

SCHEDULE OF ASSESSMENTS

Procedure/Assessments	Screening Visit [15]	Treatment Phase			Follow-Up		Unscheduled Visit [17]
Visit	1	2		3	4	5	
Day	Day -2 ~ 1	Day 1 (Baseline)	Day 2 ~ Day 6	Day 7 (EOT)	Day 15	Day 29 (ET/EOS)	
Window Period (Day)				± 1	± 2	± 3	NA
Informed Consent [1]	X						
Eligibility Evaluation	X						
Pneumonia severity index	X						
Rapid diagnostic test [12]	X						
Subject Demographics	X						
Medical History [2]	X	X					
Physical Examination (including body weight and height) [3]	X	X		X	X	X	Per investigator's decision
Vital Signs [4]	X	X		X	X	X	
Assessment of health status using the NIAID 8-point ordinal scale [5]	X	X		X	X	X	
Pulse Oxygen Saturation for SpO_2/FiO_2 ratio	X	X		X	X	X	
12-lead ECG	X [16]			X	X	X	
Chest X-ray	X [16]			X	X	X	
Laboratory Tests:							
Hematology [6]	X	X		X	X	X	
Blood Chemistry [7]	X	X		X	X	X	
Coagulation [8]	X	X		X	X	X	
Serum/Urine Pregnancy Test [9]	X			X		X [9#]	
Urinalysis [10]	X	X		X	X	X	
Biomarker evaluations [11]		X		X	X	X	
RT-PCR [12]		X		X		X [12#]	
Randomization		X					
CX-4945/Placebo Administration		X [13] 400 mg BID	X [13] 400 mg BID				
Dispense study drug		X					X [18]
Return un-used drug				X			X [18]
ePRO [14]		X	X	X	X	X	
SOC/Supportive care		X (as needed)					
Mortality Status		X	X	X	X	X	X
Hospitalization events		X	X	X	X	X	X

Procedure/Assessments	Screening Visit [15]	Treatment Phase			Follow-Up		Unscheduled Visit [17]
Visit	1	2		3	4	5	
Day	Day -2 ~ 1	Day 1 (Baseline)	Day 2 ~ Day 6	Day 7 (EOT)	Day 15	Day 29 (ET/EOS)	
Window Period (Day)				± 1	± 2	± 3	NA
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X

***Abbreviations**: BID = bis in die, twice a day; ECG = Electrocardiogram; EOT = end of treatment; ET = early termination; EOS = end of study; ePRO = electronic Patient Reported Outcomes; FiO_2 = fraction of inspired oxygen; SpO2 = saturation of peripheral oxygen; NA = not applicable.*

[1] Informed consent must be obtained prior to patient participation in any protocol-related activities that are not part of routine care. The results obtained from the routine care and associated tests performed within 24 hours before signing informed consent may be collected and utilized as Visit 1 data in this study (Protocol No. CX-4945-011). Additionally, body temperature measurements that fully meet protocol requirements but are taken within 24 hours before signing informed consent can be collected.

[2] Medical history and current therapies (medications and procedures) will be included up to 2 weeks prior to screening visit. Any pre-treatment medical events will be recorded as medical history.

[3] A complete physical exam will be performed. Height and weight should be recorded at screening visit (Visit 1) only.

[4] Vital signs, including blood pressure, pulse rate, respiration rate, and body temperature, will be evaluated at each clinic visit. In addition, subjects will self-report their body temperature by using ePRO [14] from Day 1 to Day 7 or beyond, as needed, with the temperature being measured four times daily at 4 to 6-hour intervals.

[5] Assessment of health status using the NIAID 8-point ordinal scale will be conducted on Screening, Days 1, 7, 15, and 29.

[6] Hematology: hemoglobin (Hb), hematocrit (Hct), red blood cells (RBC), white blood cells (WBC), differential of leukocytes, absolute neutrophil count (ANC) and platelets.

[7] Blood Chemistry:

- Hepatic function indicators: total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin
- Renal function indicators: blood urea nitrogen (BUN), serum creatinine, and estimated Glomerular filtration rate (eGFR)
- Electrolytes: sodium, potassium, chloride, total calcium and bicarbonate

[8] Coagulation: Prothrombin time (PT) and international normalized ratio (INR)

[9] ONLY performed on women of childbearing potential. # ONLY performed when early termination occurs before the completion of Visit 3.

[10] Urinalysis: color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, and microscopic examination of urine sediment.

[redacted] Evaluated biomarkers will include: [redacted]

[12] Swabs will be used for rapid diagnostic test, RT-PCR for presence of viral RNA (qualitative tests), Ct value and viral load:

- At Screening, perform a rapid diagnostic test for SARS-CoV-2 or influenza virus infection using a nasopharyngeal specimen.
- Nasopharyngeal swab for RT-PCR should be collected on Day 1 and Day 7.

ONLY performed when early termination occurs before the completion of Visit 3.

[13] Baseline assessments (on Day 1) should be conducted prior to administering the first dose of CX-4945 or placebo. Drug administration is twice daily for 5 consecutive days, starting on Day 1 and completing on Day 5, or on Day 6 if only one dose is administered on Day 1.

[14] Patients will be instructed on the use of the Electronic Patient Reported Outcomes (ePRO) for all dose administrations and body temperature record [4] at Visit 2. Site staff will check the completeness of ePRO at Visit 3 and Visit 4, and if necessary, at Visit 5. Patients may record dose administration on Day 1 ~ Day 6 and body temperature on Day 1 ~ Day 7 or beyond, as needed.

[15] Visit 1 and Visit 2 could be the same day. When Visit 1 and Visit 2 occur on the same day, the same assessments from Visit 2 can be omitted.

[16] The results acquired from Visit 1 should serve as the baseline for the Chest X-ray and 12-lead ECG.

[17] Adverse events, concomitant medications and hospitalization events will be recorded at an unscheduled visit (UV); other assessments will be performed at the investigator's discretion.

[18] If the subjects have lost IPs, only one more dispensation of the investigational product is allowed per subject based on the pharmacy manual.

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LIST OF ABBREVIATIONS

Abbreviations	Terms and Definitions
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC	Area Under Curve
ATC	Anatomic Therapeutic Classification
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CAP	Community-Acquired Pneumonia
[redacted]	[redacted]
CARDS	Acute respiratory distress syndrome
[redacted]	[redacted]
CHF	Congestive heart failure
CI	Confidence interval
CK2	Casein kinase II
CKD	Chronic kidney disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
[redacted]	[redacted]
Ct	Cycle threshold value
CTCAE	Common Terminology Criteria for Adverse Events
DM	Diabetes mellitus
ECF	Extended care facility
ECG	Electrocardiography
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic data capture
eGFR	Estimated Glomerular filtration rate
ePRO	Electronic Patient Reported Outcome
EOS	End Of Study
EOT	End of treatment
ET	Early termination
FAS	Full Analysis Set
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HB	Hemoglobin
Hct	Hematocrit
HEENT	Head, ears, eyes, nose, throat
[redacted]	[redacted]
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
ID	Identification
IEC	Independent Ethics Committee

Abbreviations	Terms and Definitions
[redacted]	[redacted]
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
LDH	lactate dehydrogenase
LOCF	Last Observation Carry Forward
MedDRA	Medical Dictionary for Regulatory Activities
mTOR	Mechanistic target of rapamycin
NCS	No clinical significance
NLR	Neutrophil to lymphocyte ratio
NIAID	National Institute of Allergy and Infectious Diseases
PLR	Platelet-to-lymphocyte ratio
PPS	Per Protocol Set
PRO	Patient Reported Outcome
PSI	Pneumonia Severity Index
PT	Prothrombin time
QD	Quaque die
RBC	Red blood cells
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious Adverse Event
SAF	Safety population
SHH	Sonic Hedgehog
SpO_2	Saturation of Peripheral Oxygen
STAT3	Signal transducer and activator of transcription 3
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment emergent adverse events
TESAE	Treatment-emergent serious adverse event
TFDA	Taiwan Food and Drug Administration
[redacted]	[redacted]
ULN	Upper limit of normal
WBC	White blood cells

1. INTRODUCTION

Community-acquired pneumonia (CAP) is a serious clinical problem which refers to an acute infection of the pulmonary parenchyma acquired outside of the hospital. The worldwide incidence of community-acquired pneumonia varies between 1.5 to 14 cases per 1000 person-years. The mortality rate is as high as 6% for hospitalized patients and 23% for patients admitted to the intensive care unit. The elderly adults ≥ 65 years-old with comorbidities have a higher risk of CAP, with a 2% hospitalization rate. In WHO 2020 report, 15% of children <5 years of age die from pneumonia. Moreover, immunocompromised patients have also an increased risk in CAP than general population. Lifestyle factors also affect the risk factors of CAP, including smoking, high alcohol consumption, being underweight, poor oral hygiene and frequent contact with children. [1,2,3]

The clinical presentation of CAP varies, ranging from mild symptoms that are fever, chills, cough productive of purulent sputum, dyspnea, pleuritic chest pain, and weight loss to severe symptoms that characterized by respiratory distress and sepsis.[1,2] In elder patients, more frequently symptoms present in confusion or worsening of pre-existing conditions, and without chest signs or fever.[4]

The cause of CAP could be a range of bacteria and virus. The most frequently detected pathogens in patients with CAP is *Streptococcus pneumoniae* (pneumococcus, about 30% to 35% of cases in the US and Europe [4]) and respiratory viruses (around 22% cases[5]). However, the microbial etiology of CAP could not be detected in ~50% of patients due to the failure to obtain an adequate culture sample before the initiation of therapy, and the inconsistent availability of newly improved molecular tests.

Viral pneumonia is common in the very young and in the elderly patients, while a steep decline in the incidence of viral pneumonia was observed from adolescence to 50~60 years-old patients, except people with immunosuppression.[6] However, the epidemiological condition varies by pandemic season and region, such as flu epidemics or coronavirus disease 2019 (COVID-19) pandemics. Viral pneumonia generally occurs in 3 kinds of mechanisms: (1) viral particles would inoculate directly into the lung (e.g., respiratory syncytial virus (RSV) or influenza); (2) virus spread in a contiguous fashion from viral infection to upper respiratory tract (e.g., measles); and (3) hematogenous spread from a distant viral infection (e.g., cytomegalovirus). [6] Sometimes, viral respiratory tract infections could lead to primary viral pneumonias and also predispose to secondary bacterial pneumonias. The availability of PCR-based multiplex tests enables the simultaneous identification of a wide number of viruses in viral pneumonia diagnosis. At least 26 viruses associated with CAP have now been identified that most pronounced is influenza virus infection. RSV is the predominant viral pathogen in the severe CAP. [6,7] In a meta-analysis study in 2016 wrote by M Burk *et al.* for CAP patient associated with viral infection

by using PCR identification, 31 researches (10762 subjects) were included. Of these researches, 24.5% (95% confidence interval (CI): 21.5-27.5%) patients have viral infection, 10% (95% CI: 8–11%) patients were revealed dual bacterial and viral infection. The most common identified viruses were influenza (8%), followed by rhinovirus (5.7%), coronavirus (3.3%), and respiratory syncytial virus (2.2%). There was no statistical significance among viral infection in short-term mortality, but the odds of death were significantly higher compared with patients without dual infection (OR: 2.1, 95% CI: 1.32–3.31; p=0.002; I^2 =0%).[8] In the recent year, ongoing outbreak of COVID-19 is reporting high mortality and morbidity in the world. People from all age groups are susceptible to SARS-CoV-2; however, the proportion of SARS-CoV-2 infection in children is lower than that of adults. Severe COVID-19 pneumonia is a huge challenge in clinical management. [9] For people hospitalized with covid-19, 15-30% will go on to develop covid-19 associated acute respiratory distress syndrome (CARDS) that they require ventilatory support.[10]

1.1. Introduction for Silmitasertib (CX-4945)

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

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

- CX-4945 demonstrated strong anti-viral efficacy in human cells infected by SARS-CoV-2 (pre-clinical *in vitro* study)[11]
- CX-4945 significantly reduced replication of human papillomavirus *in vivo*[12]
- In several pre-clinical and clinical trials in the diseases driven by pro-inflammatory cytokines CX-4945 demonstrated ability to significantly reduce plasma level of interleukins (IL-6, IL-8, IL-17) *in vitro* and in *vivo* (inflammatory breast cancer, Alzheimer's disease, autoimmune encephalomyelitis).[13]
- CK2 inhibitor down-regulated replication, budding and release of influenza virus in preclinical studies[14]

- CK2 inhibitor reduced phosphorylation dependent ICP27 protein export, which is necessary for its ability to export herpes simplex viral RNAs[15]
- CX-4945 also demonstrated anti-tumor activity in a variety of primary human xenografts and tumor cell line xenograft models and in clinical trials

1.2. Clinical Experience

1.2.1. COVID-19 studies

CX-4945 may 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 COVID-19 infection, thereby preventing disease progression and improving clinical outcomes.

CX-4945 was used for COVID-19 treatment in a phase I dose selection study (Protocol number: CX4945-AV04-phase I) and a phase II study (Protocol number: CX4945-AV01-IIT) under IND 152726.

In the phase I study, 30 healthy subjects were randomized into 200mg QD, 200mg BID, and 400mg BID cohorts, respectively, with 1:1:1 allocation. The total duration of the treatment was 5 days. Subjects were followed up on Day 14 after the start of the treatment. A total of 7 TEAEs in 7 subjects (23.33%) were reported as drug-related TEAEs. The most common drug-related TEAEs were diarrhea in 5 subjects in 400mg BID cohort and 1 subject in 200mg BID cohort. All of the drug-related TEAEs were mild. During study period, no treatment-emergent serious adverse event (TESAE) or death was reported. In clinical laboratory evaluations, vital signs, physical examinations, and 12-lead ECGs evaluations, no clinical significant finding was observed. Therefore, all dosing regimens (200mg QD, 200mg BID, or 400mg BID) were safe and well-tolerated.[16]

In the phase II study, a randomized, multi-center, two-arm parallel-group controlled interventional prospective study in subjects with moderate COVID-19 was conducted. Total 20 outpatient subjects were enrolled and randomized in a 1:1 ratio in two groups, including 10 subjects in CX-4945 in combination with SOC and 10 subjects in SOC only. CX-4945 1000 mg BID for 14 days was applied. In terms of COVID-19 history, mean (SD) duration of the 20 subjects were 2.8 (2.24) days with mean symptom duration of 6.3 (2.95) days. None of these subjects had COVID-19 vaccination history. In the safety results, five subjects suffered treatment related AEs in CX-4945 group, but none of these AEs were equal or greater than Grade 3. Only 2 subjects experienced SAEs and 3 subjects underwent Grade $\geq$ 3 AEs in the study, but all of which were drug-unrelated. Neither death nor Suspected Unexpected Serious Adverse Reaction (SUSAR) was reported through the study. Several clinical

significant laboratory values were detected, and most of them returned to normal or no clinical significance (NCS).[17]

With respective to time to clinical signs normalization, subjects in CX-4945 group had a median time of 7 (95% CI:1.0 ~ .) compared to SOC group of 11 (95% CI: 5.0 ~ 16.0). With regard to time to COVID-19-related symptom recovery, subjects receiving CX-4945 had a median time of 7 (95% CI:4.0 ~ 12.0) compared to 14 (95% CI:7.0 ~) of SOC group. In terms of time to oxygen saturation level normalization, subjects in CX-4945 group had a mean time of 1 compared to SOC group of 1 (95% CI:1.0 ~ 5.0). In terms of investigation of clinical benefit by EQ-D5-5L and NIAID 8-Point Clinical Progression Outcomes Scale, no significant difference was found between the two groups. No significant difference was detected on viral load and viral clearance proportion between two groups except for Day 8. Regarding changes in inflammatory markers, almost all results of two treatment groups were normal or NCS except for some due to medical history or AEs.[17]

1.2.2. Cholangiocarcinoma study

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.

Several phase I and II clinical trials of CX-4945 in cancer patients have been completed to date (e.g., solid tumors, multiple myeloma, and cholangiocarcinoma), and there is one ongoing phase I study (basal cell carcinoma; protocol number: CX-4945-07) under IND 102181 and one ongoing phase II studies (medulloblastoma; protocol number: PBTC-053) under IND 137563.

In a phase 1b/2 study (Protocol number: S4-13-001) under the US IND 144857, the subjects received CX-4945 1000 mg BID for 10 days with gemcitabine and cisplatin (G+C) on Days 1 and 8 of a 21-day cycle (n =55) or gemcitabine and cisplatin only (n =29). The median PFS was 11.2 months (95% CI, 7.6, 14.7) in CX-4945 with G+C group and 5.8 months (95% CI, 3.1, not evaluable [NE]) (p = 0.0496) in G+C only group. The median overall survival was 17.4 months (95% CI, 13.4, 25.7) in CX-4945 with G+C group versus 14.9 months (95% CI, 9.9, NE) in G+C only group. The overall response rate and disease control rate was 34.0% versus 30.8%, 86.0% versus 88.5% with CX-4945 with G+C versus G+C only groups, respectively. The most common TEAEs (all grades) with CX-4945/G+C versus G+C were diarrhea (70% versus 13%), nausea (59% vs. 30%), fatigue (47% vs. 47%), vomiting (39% vs. 7%), and anemia (39% vs. 30%).[18]

1.3. Study Rationale

Silmitasertib (CX-4945) is an inhibitor of the protein kinase CK2 (CK2, also known as casein kinase 2). It exhibits both antiviral and anti-inflammatory properties against COVID-19 *in vitro*, and showcasing its potential to improve the time to clinical signs normalization and time to COVID-19-related symptom recovery (CX4945-AV01-IIT; US IND 152726). CK2 modulates inflammatory pathways, including [redacted]. Inhibition of CK2 by CX-4945 diminishes the secretion of [redacted] stimulated with NiSO4 (Bourayne et al., 2017).[20] Hence, CX-4945 offers potential against viral infections and may moderate the elevated cytokine release during inflammation. We aim to further investigate the safety and efficacy of Silmitasertib (CX-4945) in combination with standard of care (SOC) for treating patients with community-acquired pneumonia (CAP) associated with SARS-CoV-2 and influenza viral infections.

This is a Phase II multi-center, double-blind, randomized, interventional study in approximately 120 subjects to evaluate clinical benefit of CX-4945 in adult outpatients with SARS-CoV-2 and influenza viral infection-associated pneumonia. The study will compare the efficacy of SOC combined with CX-4945 against SOC paired with a placebo, utilizing a 1:1 allocation ratio. CX-4945 will be administered at 400 mg BID for up to 5 days. This dose derives from one completed Phase I studies wherein healthy volunteers were administered CX-4945 at increment doses of 200 mg QD, 200 mg BID and 400 mg BID over a span of 5 days. The purpose of this trial is to investigate whether intervention with Silmitasertib (CX-4945) prevents the progression of CAP and moderates the elevated cytokine release associated with SARS-CoV-2 and influenza virus infection.

2. Study Objectives & Endpoints

2.1. Primary Objective and Endpoint

Primary Objective	Primary Endpoint
To evaluate the effect of intervention with Silmitasertib (CX-4945) in addition to SOC, compared to placebo plus SOC, in preventing the progression of CAP associated with SARS-CoV-2 and influenza virus infection	• The percentage of subjects requiring hospitalization, emergency room visits, or resulting in death due to progression of CAP related to SARS-CoV-2 or influenza. (Time Frame: Day 1 to Day 29)

2.2. Secondary Objective and Endpoint

Secondary Objectives	Secondary Endpoints
To evaluate the effect of intervention with Silmitasertib (CX-4945) in addition to SOC, compared with placebo plus SOC, in enhancing the subject's clinical condition	• The percentage of subjects with all cause hospitalization, emergency room visits, or death during study period (Time Frame: Day 1 to Day 29) • The percentage of subjects with improved pulmonary X-ray findings for pneumonia, relative to baseline or showing a return to normalcy (Time Frame: Baseline to Day 7, 15, and 29) • Time to symptom resolution for fever The symptom resolution for fever will be defined as body temperature lower than the following definition for 24 hours (ear temperature < 38°C, base of the tongue temperature < 37.5°C, or axillary temperature < 37°C) • Change from baseline in SpO_2/FiO_2 ratio (Time Frame: Day 1 to Day 7, 15, and 29) • The percentage of subjects exhibiting disease progression in health status Disease progression is defined as an increase of score on the

Secondary Objectives	Secondary Endpoints
	National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale. (Time Frame: Day 1 to Day 7, 15, and 29) • The percentage of subjects exhibiting health improvement in health status Health improvement is defined as a reduction of score on the NIAID 8-point ordinal scale. (Time Frame: Day 1 to Day 7, 15, and 29)
To evaluate the effect of intervention with Silmitasertib (CX-4945) in addition to SOC, compared with placebo plus SOC, on reducing viral presence	• The percentage of subjects with a negative RT-PCR result for the SARS-CoV-2 (only for SARS-CoV-2 domain) or the influenza virus (only for influenza virus domain) on Day 7 FilmArray data (Negative/Positive) obtained from Protocol v.1.0 will be integrated into and considered equivalent to the results for RT-PCR. (Time Frame: Day 1 to Day 7) • Change from baseline in viral load in nasal secretions by RT-PCR (only for SARS-CoV-2 domain) (Time Frame: Day 1 to Day 7) • Change from baseline in Ct values (only for SARS-CoV-2 domain) (Time Frame: Day 1 to Day 7)
To evaluate the safety and tolerability of Silmitasertib (CX-4945)	• TEAEs and SAEs (Time Frame: Day 1 to Day 29) • Laboratory test (Time Frame: Day 1 to Day 29) • Vital signs (Time Frame: Day 1 to Day 29) • Electrocardiogram (ECG) results (Time Frame: Baseline to Day 29)

2.3. Exploratory Objectives and Endpoints

Exploratory Objectives	Exploratory Endpoints
To evaluate the effect of intervention with Silmitasertib (CX-4945) in addition to SOC, compared with placebo plus SOC, on inflammatory status	• The percentage of subjects achieving normalized [redacted] levels on Day 7 This statistical analysis will only be conducted in subjects whose [redacted] levels exceed the upper limit of normal (ULN) at Visit 2. (Time Frame: Day 7) • Change from baseline in [redacted] (Time Frame: Day 1 to Day 7, 15, and 29) *Note: If the flow cytometry analyses for [redacted] are not performed at the local site lab, the related endpoint be omitted.*
To evaluate the effect of intervention with Silmitasertib (CX-4945) in addition to SOC, compared with placebo plus SOC, on moderating the elevated cytokine release associated with SARS-CoV-2 and Influenza virus infection	[redacted]Changes from baseline in serum cytokine levels: Cytokines to be quantified; [redacted] (Time Frame: Day 1 to Day 7, 15, and 29)

3. STUDY DESIGN

3.1. Overall Study Design

This is a Phase II, multi-center, double-blind, randomized, interventional study in approximately 120 subjects to evaluate clinical benefit of CX-4945 in adult outpatients with SARS-CoV-2 and influenza viral infection-associated pneumonia. The subjects will be recruited into two domains, including SARS-CoV-2 and Influenza virus domains. The study will compare the efficacy of SOC combined with CX-4945 against SOC paired with a placebo, utilizing a 1:1 allocation ratio in each domain. The study arms will be listed below:

Domain I: SARS-CoV-2 domain

Arm 1: CX-4945 (400 mg BID for 5 days) + SOC

Arm 2: Placebo + SOC

Domain II: Influenza virus domain

Arm 3: CX-4945 (400 mg BID for 5 days) + SOC

Arm 4: Placebo + SOC

Screening visit will collect health information and perform protocol-specified tests to determine patients' eligibility. After screening visit, eligible subjects who fulfill all selection criteria for enrollment will be randomized into each of the arms. The CX-4945 will be administered at 400 mg BID for 5 days. Subjects will be followed up until Day 29.

Subjects will return to clinics site for 5 designated visits: Visit 1 (Day -2~1, screening), Visit 2 (Day 1, baseline, randomization, the start of treatment), Visit 3 (Day 7 ± 1, the end of treatment), Visit 4 (Day 15 ± 2, 1st follow-up), and Visit 5 (Day 29 ± 3, 2nd follow-up, the end of study). The hospitalization and emergency visit due to CAP related to SARS-CoV-2 or influenza infection, chest X-ray, body temperature, pulse oxygen saturation for SpO_2/FiO_2 ratio will be monitored. RT-PCR will be performed to assess the reduction of viral presence and to measure viral load (SARS-CoV-2 only). Safety issues, including 12-lead ECG, laboratory test, vital signs, and adverse events will be evaluated after treatments during study period.

3.2. Study Population

3.2.1. Subject number

A total of 120 evaluable subjects (= modified Per-Protocol population) will be enrolled into the study.

The subjects in each domain will be randomized with 1:1 allocation ratio into active drug plus SOC arm and placebo plus SOC arm. The study arms will be as the following:

Domain I: SARS-CoV-2 domain

Arm 1: CX-4945 (400 mg BID for 5 days) + SOC

Arm 2: Placebo + SOC

Note: The SOC within the SARS-CoV-2 domain is defined as the medications in use at each respective site for the treatment of CAP related to SARS-CoV-2 infection.

Domain II: Influenza virus domain

Arm 3: CX-4945 (400 mg BID for 5 days) + SOC

Arm 4: Placebo + SOC

Note: The SOC within the influenza virus domain is defined as the medications in use at each respective site for the treatment of CAP related to influenza virus infection.

3.2.2. Inclusion criteria

Subjects meeting all of the following criteria will be considered for enrollment into the study:

1. Not currently hospitalized
2. Males or females aged ≥ 18 years at the time of signing the informed consent form (ICF)
3. Patients diagnosed with viral pneumonia, as determined by the investigator, who exhibit any of the subsequent criteria: presence of respiratory symptoms or fever (ear temperature ≥ 38 °C, base of the tongue temperature ≥ 37.5 °C, or axillary temperature ≥ 37 °C)
4. With a pneumonia severity index (PSI) of risk class II or III
5. Oxygen saturation measured by pulse oximetry (SpO_2) ≥94% on room air at sea level
6. Positive test for SARS-CoV-2 or influenza virus infection, confirmed by rapid diagnostic test (excluding cases where both SARS-CoV-2 and influenza virus are positive)
7. Confirmed lower respiratory tract infection by X-ray
8. At screening, subjects capable of childbearing must provide a negative serum or urine pregnancy test. These subjects must also commit to adhering to the study-specified contraceptive methods throughout the study duration

Notes: Acceptable contraceptive methods include:

- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps)

9. The participant (or legal representative) agrees and is able to adhere to study protocol-stated requirements, instructions, and restrictions in the investigator's judgement. Furthermore, the participant is capable of understanding and has signed the IRB-approved Informed Consent Form (ICF)
10. With at least two of the risk factors listed below:

    Age $\geq$ 50 years-old; cancer and a life expectancy of $\geq$ 6 months; HIV infection; immunocompromised patient; congestive heart failure (CHF), or coronary artery disease (CAD), or cardiomyopathies; chronic kidney disease (CKD); chronic liver disease; chronic lung disease; diabetes mellitus (DM); body mass index (BMI) > 25 kg/m^2; asthma; cerebrovascular disease; cystic fibrosis; dementia; or current and former smoker

3.2.3. Exclusion criteria

1. Subject received investigational treatment within 30 days prior to the study, or concurrent use of another investigational drug
2. Subject has a history of severe renal disease (required phosphate binders or dialysis)
3. Subject has chronic diarrhea, characterized by three or more loose stools daily for a minimum of four weeks
4. High likelihood of mortality within the next 48 hours, as assessed by the investigator
5. Subject showing signs of respiratory failure and mechanical ventilation is required
6. Subject with liver cirrhosis
7. Subject with hepatitis B and/or hepatitis C disease, unless the subject has an aspartate aminotransferase (AST) level ranging from 8 to 31 U/L and an alanine aminotransferase (ALT) level from 0 to 41 U/L
8. Known active tuberculosis
9. Current documented bacterial infection
10. Subject has a documented anaphylactic reaction, regardless of cause

11. Subject who has taken an antiviral agent against respiratory viral infection for a continuous duration of more than 24 hours before screening
12. Subject is with active gastrointestinal diseases including gastritis, ulcerative colitis, Crohn's disease, or hemorrhagic coloproctitis
13. Subjects received warfarin within 14 days prior to screening or intend to during the screening or treatment phase
14. History of allergic reactions to any of the ingredients or components used in the manufacture of CX-4945
15. Women who are pregnant or breastfeeding, or planning pregnancy during the study

    Note: Men and women of reproductive potential must commit to effective contraception methods or abstinence during the study. Any resulting pregnancies or suspected pregnancies must be reported to the treating physician immediately.
16. ALT or AST levels > 5 times upper limit of normal (ULN)
17. eGFR < 30 mL/min/1.73m^2 (calculated by the MDRD formula)
18. Absolute neutrophil count (ANC) <1000/μL
19. Have received treatment with a SARS-CoV-2 specific monoclonal antibody
20. Have received convalescent COVID-19 plasma treatment
21. Concurrent use of baricitinib
22. Any physical findings or illness history that may compromise study results or increase patient risk, as determined by the investigator.

3.3. Screen failure

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

3.4. Discontinuation of Study Intervention

Discontinuation of study product CX-4945/placebo does not mean discontinuation from the study, and the remaining study procedures will be completed as designated by this protocol. If a clinically significant finding is identified following the initiation of study treatment, the Investigator (or designee) will determine if any change in subject management is necessary. However, a subject should be discontinued from study product CX-4945/placebo in any of the following circumstances:

- A suspected Grade 3 or higher treatment-related AE (according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0)
- Any treatment-related SAE
- A subject receives baricitinib
- A subject receives warfarin
- The subject is pregnant

3.5. Discontinuation/Withdrawal from the Study

Subjects will be followed and monitored over the course of the study stated in **Section 5.1** Visit Schedule. If a subject does not attend any of the regularly scheduled visits, the subject will not be deemed as withdrawn, but the missed visit(s) will be considered as missing data in the study registry. Subjects may be discontinued from study product CX-4945 (**Section 3.4**) at the discretion of the Investigator if any severe, untoward effects occur to the subjects during the treatment phase. However, subjects may not be terminated from the study because of AEs.

If a subject, whether continuing study product CX-4945 or not, fails to return to any scheduled visits (i.e., lost to follow-up), or if the Investigator determines that it is in subject's best interest to be prematurely withdrawn from the study, the Investigator must determine the primary reason for subject's premature withdrawal and document this incidence in the eCRF, including the date of occurrence and the reason(s). All study-related information collected prior to subject's withdrawal will be retained and maintained in the study analysis unless otherwise explicitly requested by the subject; however, no further efforts will be made to obtain or record additional medical information about the subject. Subjects will be withdrawn from the study prematurely due to any of the following circumstances:

- Subject (or legal representative) decides to withdraw consent at any time.
- Subject, determined by the Investigator (or designee), is no longer physically or mentally feasible for further participation in the study.
- Subject is lost to follow-up.

- The sponsor terminates the study.

All collected/generated data and information about the subjects in the study prior to the time of study discontinuation will be recorded and analyzed, including the date and reason(s) to discontinue the study.

All subjects who have received at least one dose of study medication will be encouraged to complete all tests scheduled for the ET wherever possible at the time of the subject's withdrawal within 7 days.

3.6. Method of Assigning Subjects to Treatment Groups

The study treatment will be randomly assigned to subjects. The randomized sequence of study treatments will be generated by a qualified biostatistician. The randomization schedule will be kept and maintained by the designated personnel before the study begins and until the database lock. The biostatistician prepares the schedule with a 1:1 randomization ratio (CX-4945: Placebo) by stratified randomization with study domains and study sites strata. Also, block permutation is used for generating randomization schedule. Eligible subjects will receive a random number at randomization. The subject will receive the corresponding treatment assigned by the EDC system. For any reason that a subject withdraws from the study prematurely after the randomization, his/her randomization number will not be reused. The next eligible subject will receive the lowest available randomization number.

3.7. Blinding

This is a double-blind study. Neither the subject nor the investigators, clinic administrators, or sponsor staff who involve in the treatment or clinical evaluation of the subjects will be aware of the treatment received either at the time of randomization or later, throughout the conduct of the trial. Assigned unblinded team may include study site stuff, CRO's personnel and/or Senhwa Biosciences, Inc's personnel. Other personnels involved in the study (the investigator and the clinical monitor) will be blinded until the database lock.

The treatment codes will not be prematurely broken unless an emergency situation, when the appropriate management of the subject necessitated acknowledgement of the treatment allocation, occurred. In the event of a medical emergency, if possible, the medical monitor should be contacted first to discuss the need for unblinding. For unblinding a subject, the treatment code blind can be obtained by the investigator, by accessing the EDC system.

The sponsor must be notified immediately if the treatment code blind is broken.

3.8. Concomitant Therapy

1. The following medication should be prohibited during the specified period:
   (1) Warfarin is prohibited 14 days prior to screening and the treatment phase.
   (2) Any other investigational treatment within 30 days before Screening and during study
2. The routine use of antibiotics is not recommended. Antibiotics may be used if bacterial infections are present or suspected. The type of antibiotic will be selected based on the subject's clinical disease status and symptoms with discretion of investigator.

4. TREATMENTS

4.1. Detail of Study Medication

4.1.1. Active drug

Study medication	CX-4945
Characteristics & Physical State	The isolated CX-4945 Sodium Salt is pale yellow to yellow solid which is formulated in an opaque blue, shell-gelatin capsule.
Dose(s)	200 mg/capsule
Dosage and Frequency	CX-4945 will be administered at 400 mg BID for 5 consecutive days starting on Day 1 in addition to SOC.
Administration route	Immediate release, oral administration
Mechanism of Action	CX-4945 is an inhibitor of Casein Kinase II (CK2) with anti-viral and anti-inflammatory effects. It interacts competitively with the ATP-binding site of CK2 subunit alpha, leading to the inhibition of several downstream signaling pathways.
Pharmacological category	Antiviral Drug
Storage	Store at temperature between 15-30°C.
Manufacturer	Senhwa Biosciences, Inc.

4.1.2. Placebo drug

Study medication:	CX-4945 Placebo
Characteristics & Physical State	The placebo drug is identical in appearance to the CX-4945 with the same excipient ingredients, but without the active compound.
Dose(s)	200 mg/capsule
Dosage and Frequency	The dosage and frequency are the same as active drug.
Administration route	Immediate release, oral administration
Storage	Store at temperature between 15-30°C.
Manufacturer	Senhwa Biosciences, Inc.

4.2. Dosage and Administration

Subjects will take two capsules of 200 mg CX-4945 or placebo, along with water twice daily on an empty stomach (preferably two hours after finishing a meal). It is recommended to take one capsule at a time with a 10-minute interval between each capsule to avoid a clumping effect. After taking the capsules, subjects are encouraged to avoid food intake, except for water, for at least 2 hours.

4.3. Packaging and Labeling

Packaging: CX-4945 are supplied as 200 mg strength auto-filled capsules (AFCs) in size 1, opaque blue capsules. Seventy (70) CX-4945 capsules (or placebo) are packaged in a 120 cc wide mouth round white HDPE bottle with a 38 mm cap with induction seal. The bottle contains a polyester coil and 1 g Sorb-IT® desiccant. Senhwa Biosciences will arrange the preparation, packaging and distribution of the study drugs.

Labeling: All study medication will be supplied in identical package, and the label will include the required regulatory agency caution statements, the protocol number, the Sponsor's identification, manufacturer's name, storage conditions, and expiry date.

4.4. Handling and Storage

The study medication will be handled by the investigator or the designated pharmacist for management and dispensation. All supplies for this study should be kept under adequate security and storage conditions. CX-4945 should be stored in the container provided, between 15 °C and 30 °C, as indicated on the label, and should be protected from moisture, freezing, and bright light

4.5. Supplies and Accountability

The investigator or the pharmacist will inventory and acknowledge receipt of all shipments of study medication. All study medication must be kept in a locked area with access restricted to designated study personnel. The study medication must be stored in accordance with the manufacturer's instructions. The investigator or pharmacist will also keep accurate records of the quantities of study medication dispensed and used by each subject. The site monitor will periodically check the supplies of study medication held by the investigator or the pharmacist to ensure accountability of all study medication used.

4.6. Treatment Compliance

Site staff will dispense study medications to all subjects ensuring proper administration of the investigational product (IP). Patients will be instructed on using ePRO to keep a dosing record for all dose administrations. Patients will be instructed to bring the dosing record and all unused study medication and empty study medication containers at Visit 3. The dosing record will be reviewed and the IP will be counted, documented, and recorded by site staff. The investigator or sub-investigator will check the compliance status of each patient based on the number of prescribed IP, number of returned IP, or number of lost IP, and describe compliance status in the medical record or other source documents, as well as checking data integrity in reference to the IP inventory at each visit.

5. STUDY CONDUCT

5.1. Visit Schedule

5.1.1. Visit 1 – Screening Visit (Day -2 ~ 1)

After a subject has signed the informed consent document, he or she will be enrolled after screening for selection criteria. The following assessments should be evaluated at this visit:

(1) Obtain signed informed consent
(2) Check subject's eligibility: inclusion and exclusion criteria
(3) Collect demographic data
(4) Collect general medical history
(5) Conduct physical exam: It should be also recorded a complete physical exam, height, and weight
(6) Measure vital signs
(7) Collect NIAID 8-point ordinal scale
(8) Assess pulse oxygen saturation: measure SpO_2 and record FiO_2
(9) Perform 12-lead ECG
(10) Perform chest X-ray
(11) Collect urine and blood samples for the following laboratory tests
    - Hematology
    - Blood Chemistry
    - Coagulation
    - Urinalysis
(12) Perform pregnancy test: Only for female with child bearing potential
(13) Record Pneumonia Severity Index (PSI) risk class
(14) Collect nasopharyngeal swab samples for rapid diagnostic test
(15) Collect prior and concomitant medications

5.1.2. Visit 2 (Day 1) – Baseline, randomization, the first day of treatment

The following procedures should be evaluated at the visit:

(1) Collect any change of medical history. Any pre-treatment medical events will be recorded as medical history
(2) Conduct physical exam

(3) Measure vital signs
(4) Collect NIAID 8-point ordinal scale
(5) Assess pulse oxygen saturation: measure SpO_2 and record FiO_2
(6) Collect urine and blood samples for the following laboratory tests.
    - Hematology
    - Blood Chemistry
    - Coagulation
    - Urinalysis
    - Biomarker evaluations
(7) Collect nasopharyngeal swab samples for RT-PCR
(8) Randomization
(9) Dispense study drug. The study drugs will be administered for 5 consecutive days starting on Day 1 and completing on Day 5, or on Day 6 if only one dose is administered on Day 1.
(10) Provide SOC/supportive care (as needed)
(11) Record any change of concomitant medication
(12) Instruct the use of the Electronic Patient Reported Outcomes (ePRO) for dose administrations and body temperature record
(13) Record hospitalization events and ER visit, if any
(14) Check mortality status
(15) Record adverse events after drug administration, if any

5.1.3. Visit 3 (Day 7 ± 1 Day) – The end of treatment (EOT)

The following assessments should be evaluated at this visit:

(1) Conduct physical exam
(2) Measure vital signs
(3) Collect NIAID 8-point ordinal scale
(4) Assess pulse oxygen saturation: measure SpO_2 and record FiO_2
(5) Perform 12-lead ECG
(6) Perform chest X-ray
(7) Collect urine and blood samples for the following laboratory tests.
    - Hematology
    - Blood Chemistry
    - Coagulation

- Urinalysis
- Biomarker evaluations

(8) Perform pregnancy test: Only for female with child bearing potential

(9) Collect nasopharyngeal swab samples for RT-PCR

(10) Check ePRO completion status

(11) Provide SOC/supportive care (as needed)

(12) Check drug accountability and compliance. Return all unused study drugs and empty containers

(13) Record hospitalization events and ER visit, if any

(14) Record any change of concomitant medication

(15) Record adverse events and check mortality status, if needed

5.1.4. Visit 4 (Day 15 ± 2 Days) – 1st Follow-up

The following assessments should be evaluated at this visit:

(1) Conduct physical exam

(2) Measure vital signs

(3) Collect NIAID 8-point ordinal scale

(4) Assess pulse oxygen saturation: measure SpO_2 and record FiO_2

(5) Perform 12-lead ECG

(6) Perform chest X-ray

(7) Collect urine and blood samples for the following laboratory tests.

- Hematology
- Blood Chemistry
- Coagulation
- Urinalysis
- Biomarker evaluations

(8) Provide SOC/supportive care (as needed)

(9) Check ePRO completion status

(10) Record hospitalization events and ER visit, if any

(11) Record any change of concomitant medication

(12) Record adverse events and check mortality status, if needed

5.1.5. Visit 5 (Day 29 ± 3 Days) – 2nd Follow-up, the end of study (EOS)/early termination (ET)

The following assessments should be evaluated at this visit:

(1) Conduct physical exam
(2) Measure vital signs
(3) Collect NIAID 8-point ordinal scale
(4) Assess pulse oxygen saturation: measure SpO_2 and record FiO_2
(5) Perform 12-lead ECG
(6) Perform chest X-ray
(7) Collect urine and blood samples for the following laboratory tests.
    - Hematology
    - Blood Chemistry
    - Coagulation
    - Urinalysis
    - Biomarker evaluations
(8) Perform pregnancy test: Only for female with child bearing potential when early termination occurs before the completion of Visit 3
(9) Collect nasopharyngeal swab samples for RT-PCR (only performed when early termination occurs before the completion of Visit 3)
(10) Provide SOC/supportive care (as needed)
(11) Check ePRO completion status (as needed)
(12) Record hospitalization events and ER visit, if any
(13) Record any change of concomitant medication
(14) Record adverse events and check mortality status, if needed

5.2. Study Assessments

5.2.1. Eligibility and informed consent

Subjects will be screened prior to the start of the study treatment. All assessments will be performed after the subjects have signed and dated the informed consent form.

The investigator or a designee will explain the nature of the study to subjects. The subject will be given an informed consent form to be read carefully before agreeing to take part in the study and before the study-specific procedures take place. The informed consent form should be reviewed, signed, and dated by the subject and the investigator. A copy of the statement will be given to the subject, and the

original should be maintained by the investigator in the site master file. After informed consent being obtained, designed procedures and assessments will be initiated to determine eligibility.

5.2.2. Demographic data, medical history, and concomitant medication

Demographic data will be collected at the screening visit. Demographic data includes birth year, age, and sex.

Any pre-treatment medical events will be recorded as medical history. The general medical history within 2 weeks before Screening Visit should be recorded at Screening Visit. The general medical history includes chronic diseases, allergic history, surgical history, and disease of interests, such as pulmonary, gastrointestinal, cardiovascular, cerebrovascular, and autoimmune events, cystic fibrosis, dementia, and acute or chronic infection. History of severe renal disease and documented anaphylactic reaction should be recorded in a lifetime basis.

Concomitant medication will be recorded when subjects received the following:

- Medication from 2 weeks prior to screening visit to end of the study
- Any investigational treatment within 30 days prior to the study
- SARS-CoV-2 specific monoclonal antibody or convalescent COVID-19 plasma treatment prior to screening

5.2.3. Pneumonia severity index

For each subject, the risk class of Pneumonia Severity Index (PSI) will be recorded. PSI is a clinical predication rule which can be used to calculate the probability of morbidity and mortality for community acquired pneumonia. It is used to predict the need for hospitalization in people with pneumonia.

Table 5-1 PSI Algorithm

Step 1: Stratify to Risk Class I vs. Risk Classes II-V	
Presence of:	
Over 50 years of age	Yes/No
Altered mental status	Yes/No
Pulse ≥125/minute	Yes/No
Respiratory rate >30/minute	Yes/No
Systolic blood pressure <90 mm Hg	Yes/No
Temperature <35 °C or ≥40 °C	Yes/No

Step 1: Stratify to Risk Class I vs. Risk Classes II-V	
History of:	
Neoplastic disease	Yes/No
Congestive heart failure	Yes/No
Cerebrovascular disease	Yes/No
Renal disease	Yes/No
Liver disease	Yes/No
If any "Yes", then proceed to Step 2 If all "No" then assign to **Risk Class I**	

Step 2: Stratify to Risk Class II vs III vs IV vs V	
Demographics	**Points Assigned**
If Male	+Age (yr)
If Female	+Age (yr) − 10
Nursing home resident	+10
Comorbidity	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical Exam Findings	
Altered mental status	+20
Pulse ≥125/minute	+10
Respiratory rate >30/minute	+20
Systolic blood pressure <90 mm Hg	+20
Temperature <35 °C or ≥40 °C	+15
Lab and Radiographic Findings	
Arterial pH <7.35	+30
Blood urea nitrogen ≥30 mg/dl (9 mmol/liter)	+20
Sodium <130 mmol/liter	+20
Glucose ≥250 mg/dl (14 mmol/liter)	+10
Hematocrit <30%	+10

Step 2: Stratify to Risk Class II vs III vs IV vs V	
Partial pressure of arterial O_2 <60mmHg	+10
Pleural effusion	+10
Σ <70 = **Risk Class II** Σ 71-90 = **Risk Class III** Σ 91-130 = **Risk Class IV** Σ >130 = **Risk Class V**	

A pneumonia severity index will be assessed at screening visit.

5.2.4. Efficacy Assessments

5.2.4.1. Hospitalization and Emergency Room Visit

If a participant is hospitalized or during emergency room (ER) visit, procedures and assessments will continue per the visit schedule. Hospitalization is defined as inpatient admission and more details are listed in **Section 5.2.5.6**. Hospitalization event will be followed up until Day 29.

This table describes discharge from hospital scenarios if an outpatient is subsequently hospitalized.

Table 5-2 Discharge from hospital (Outpatients Subsequently Hospitalized)

If hospital discharge…	**Then….**
Occurs prior to Day 29	Subjects will be asked to complete the remaining study assessments at the time points indicated in the visit schedule.
Occurs on the same day as a scheduled study visit	If the scheduled study assessments are performed during hospitalization and the circumstances meet **all** the following criteria, assessments do not need to be repeated. • The scheduled study assessments have been performed within 8 hours of discharge. • There has been no change in clinical status. • The information is available to the site.

5.2.4.2. Chest X-ray

Chest X-ray will be performed at Visits 1, 3, 4, and 5. The results obtained at Visit 1 should be baseline before the start of treatment. The findings will be evaluated by the investigators and noted as "Normal", "Abnormal, non-clinical significant (NCS)" or "Abnormal, clinical significant (CS)" with comments in the CRF/eCRF. Any clinical significant abnormal findings should be recorded as an adverse event during the study. Post-treatment pneumonia status, as assessed by the chest X-ray, will be categorized as 'Worsen', 'No Change', 'Improved' or 'Normal'.

5.2.4.3. National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale

The NIAID 8-point ordinal scale used in this study is as follows:

Table 5-3 NIAID 8-point ordinal scale

Score	Description
1	Not hospitalized with no limitation of activities
2	Not hospitalized - limitation of activities or home oxygen, or both
3	Hospitalized with no supplemental oxygen, and no ongoing medical care
4	Hospitalized with no supplemental oxygen, but with ongoing medical care
5	Hospitalized with requirement of supplemental oxygen
6	Hospitalized with need of non-invasive ventilation or high flow oxygen supplementation
7	Hospitalized with invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
8	Death

Disease severity will be evaluated using the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale. Higher score indicates deterioration in the clinical status. Disease progression is defined as an increase of score on the NIAID 8-point ordinal scale, such as from Score 1 to Score 3. Health improvement is defined as a reduction of score on the NIAID 8-point ordinal scale, such as from Score 4 to Score 2.

5.2.4.4. RT-PCR

Nasopharyngeal swabs will be used to perform RT-PCR for the following tests:

- Presence of viral RNA (qualitative result: positive or negative)

- Ct values (SARS-CoV-2 Domain only)
- Viral load (SARS-CoV-2 Domain only)

Fully validated RT-PCR tests shall be performed. RT-PCR tests for SARS-CoV-2 Domain will be conducted in the central lab, while testing for the presence of viral RNA for influenza Virus Domain will be performed at each local site lab.

5.2.4.5. Mortality status

Mortality status will be followed up until Day 29 if applicable.

5.2.4.6. Electronic Patient Reported Outcome (ePRO)

An ePRO will be used for subjects to record body temperature from Day 1 to Day 7 or beyond to confirm fever-free (as Section **5.2.5.2 Vital signs**) and the IP intake from Day 1 up to Day 6.

5.2.5. Safety Assessments

5.2.5.1. Physical examination

A complete physical examination will be performed at every visit, including the examination of general appearance, HEENT (head, ears, eyes, nose, throat), neck (including thyroid), lymph nodes, skin, cardiovascular, pulmonary, abdomen, neurological system and musculoskeletal/joints.

A complete physical examination will be performed at each visit. Height and weight will be collected at Visit 1 (Screening Visit) only.

5.2.5.2. Vital signs

The pulse rate, blood pressures in sitting position, respiratory rate, and body temperature will be assessed and recorded in clinic site at each visit. The body temperature assessed at site on Day 1 should be baseline before the start of treatment. Any clinically significant abnormal findings should be record as an adverse event during the study.

After the first dose of CX-4945 or placebo administration on Day 1, subjects will self-measure their body temperature and record it in ePRO four times a day, every 4 to 6 hours.

To confirm fever-free:

After the temperature falls below the fever definition, the subject will continue recording for a minimum of 24 hours.

5.2.5.3. Electrocardiogram

The results of ventricular rate, PR interval, QRS interval, QT interval, and RR interval will be recorded, if available. Corrected QT interval (QTc) will be calculated using Fridericia formula. ECG will be evaluated by the investigators and noted as "Normal", "Abnormal, non-clinical significant (NCS)" or "Abnormal, clinical significant (CS)" with comments in the CRF/eCRF. The test may be repeated if the original result is questionable.

5.2.5.4. Pulse oxygen saturation

Measuring the amount of oxygen-carrying hemoglobin in the blood relative to the amount of hemoglobin not carrying oxygen will be performed at each visit. Pulse oxygen saturation will be measured using a standard pulse oximeter, oxygen analyzer, or physiologic monitor. Record the FiO_2 accompanying each SpO_2 measurement. Oxygen saturation to fraction of inspired oxygen ratio (SpO_2/FiO_2) will be calculated for statistical analyses.

5.2.5.5. Laboratory test

The following laboratory analyses will be performed. Reference ranges will be used by the investigator to assess the laboratory data for clinical significance and pathological changes.

Hematology

Hemoglobin (Hb), Hematocrit (Hct), Red Blood Cells (RBC), White Blood Cells (WBC), differential of leukocytes, Absolute Neutrophil Count (ANC) and platelets.

Blood Chemistry

- Hepatic function indicators: total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin
- Renal function indicators: BUN, Serum creatinine, and eGFR
- Electrolytes: sodium, potassium, chloride, total calcium and bicarbonate

Coagulation

Prothrombin time (PT) and International Normalized Ratio (INR)

Urinalysis

Color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, and microscopic examination of urine sediment (including red blood cells, white blood cells, epithelial cells, bacteria, casts, and crystals.)

Biomarker evaluations

- Serum cytokine level: [redacted]

[redacted] Inflammatory biomarkers: [redacted]

5.2.5.6. Hospitalization events

If a subject is admitted to the hospital, the participant will remain in the study and follow the procedures outlined in the visit schedule. Hospitalization is defined as inpatient admission.

The date of hospitalization events will be recorded in the CRF and includes:

- Hospitalization
- Emergency room visit: only for dosed subjects that last 24 hours or longer will be included
- ICU admittance
- Extended care facility (ECF) admittance: ECF events will only be documented for subjects dosed in the trial who experience adverse events (AEs) and require additional medical support in the ECF, such as respiratory therapy to address the AEs. The requirement for additional medical support in the ECF is considered comparable to hospitalization as a discretion by the investigator. This means ECF events occurring before trial enrollment will not be documented. Additionally, enrolled subjects without experiencing AEs move to the ECF after enrollment will not be considered hospitalized and do not need to be entered into the EDC.
- Discharge

5.2.5.7. Clinical Status and Medications/Procedures of Special Interest

The subject's clinical status and concurrent medications/procedures of special interest will be recorded in the CRF, including the level of consciousness, limitation on activities due to CAP, and requirements for the following:

- Ongoing hospital medical care
- Supplemental oxygen
- Non-invasive ventilation or a high flow oxygen device
- Mechanical ventilation
- ECMO
- Additional organ support (e.g., pressors, renal replacement)

5.2.5.8. Respiratory Support

Once enrolled in the study, subjects may be managed with high-flow nasal cannula, noninvasive positive pressure ventilation or any other form respiratory support as needed per investigator discretion

5.2.5.9. Pregnancy test

A urine or blood pregnancy test should be performed in women of childbearing potential at screening visit and Day 7. Subject should carry out efficient birth control throughout the study period.

5.2.5.10. Treatment Emergent Adverse Events (TEAEs)

The treatment emergent adverse events will be collected from the start of treatment to the end of study. The detail of adverse event will be referred to **Section 6 Adverse Events**.

6. ADVERSE EVENTS

The treatment emergent adverse event (TEAE) and serious adverse event (SAE) will be recorded from the start of treatment until the end of study.

Any pre-treatment medical events will be recorded as medical history.

6.1. Adverse Event (AE)

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the study medication. (Definition per International Conference on Harmonization [ICH]). A medical occurrence fulfills the definition of SAE in section 6.2 is also an AE.

Except for SAEs, Adverse Events are NOT:

- Clinical events related to expected progression of COVID-19 or influenza.
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). However, the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).

6.1.1. Treatment Emergent Adverse Event (TEAE)

A treatment-emergent adverse event (TEAE) is defined as any unfavorable and unintended disease or its sign (including an abnormal laboratory value) in a subject who received the study drug, irrespective of the causal relationship with the study drug.

6.2. Serious Adverse Event (SAE)

The definition of a Serious Adverse Event (SAE) is any untoward (negative with respect to the subject's pre-operative condition) medical occurrence that:

- Results in death,
- Is life threatening (immediately as it occurred, not had it become worse at some time in the future),
- Requires hospitalization (or a prolongation of hospitalization in already hospitalized patients),
- Results in a persistent or significant disability or incapacity, or

- Is a congenital anomaly or birth defect.

There are medical events that may not require inpatient hospitalization, be immediately life threatening, or result in death but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed before. Medical and scientific judgments should be exercised in deciding whether an event should be reported as a "Serious Adverse Event."

Nevertheless, the following events will NOT be reported as a SAE:

- Hospitalization due to social reasons in absence of an adverse event
- Hospitalization due to surgery or procedure planned before entry into the study (must be documented in the CRF)
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline

6.3. Severity of Adverse Events

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (e.g., laboratory abnormalities).
The grade refers to the severity of the AE using CTCAE Version 5.0 (published on November 27, 2017). The CTCAE displays Grade 1 to 5 with unique clinical descriptions of severity for each AE as shown in below:

Table 6-1 Grading scales of AEs

Grades of AEs	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 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.

* Activities of daily living (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 medication, and not bedridden.

6.4. Associated with the Use of the Medication

An adverse event is considered associated with the use of the drug if the attribution is certain, probably/likely, possible, or unlikely by the definitions listed as follows. The causal relationship between AEs and study drug modified from WHO-UMC system for standardized case causality assessment.

Table 6-2 Causality categories between AEs and study drug

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unrelated	• Occurred before dosing • Due wholly to factors other than study treatment

6.5. Reporting Procedure

6.5.1. Adverse Event (AE)

Any AE occurring from the time the subject takes the first dose of the IP will be collected as treatment-emergent adverse events (TEAE) and the safety analysis will be carried out with TEAE. All TEAEs, regardless of seriousness, severity, or presumed relationship to study regimen, will be evaluated and recorded by investigators preferably with a diagnosis or medical terminology instead of signs, symptoms, and/or other clinical information on the TEAE form of CRF until recoverable or stable without a further follow-up by investigators' opinions. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

6.5.2. Serious Adverse Event (SAE)

As any SAE occurs, the investigator must inform sponsor or its delegate within 24 hours of their knowledge of the event by email, fax or telephone.

It is the responsibility of Investigators to review all documents (e.g., site progress notes, laboratory, and diagnostics reports) relative to the AEs/SAEs/SUSARs and record on the appropriate documents. Investigator will transmit the related copies of patient's medical records for SUSAR cases to sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to the sponsor ASAP. The sponsor should file the initial report of SUSAR to FDA/TFDA within 15 days (7 days for death or life-threatening events) after aware of the event. Completed follow-up report for death or life-threatening events must be filed within 15 days and/or till recoverable or stable without a further follow-up by investigators' opinions.
The SAE and SUSAR shall be reported promptly according to the reporting procedure of each IRB(s).

6.5.3. Pregnancy reporting

Any subject and subject's female partner who becomes pregnant during the study period should be recorded and the information regarding this pregnancy should be collected. When a subject suspects a pregnancy during the study period, a pregnancy test should be conducted. Once pregnancy is confirmed, the subject should be withdrawn from the study (**Section 3.5**). The pregnancy should be reported to the sponsor using the pregnancy report form. The Obstetrician/Gynecologist of the female subject or male subject's partner should be notified the study information. Because information of specific tests regarding this IP is not clear yet, whenever possible, a pregnancy should be followed to term or to any premature terminations reported. Additionally, the status of the mother and child should

be reported to the sponsor after delivery. Although pregnancy occurring during the study is not considered as an adverse event, abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are consider SAEs.

7. STATISTICAL METHODS

7.1. Sample Size Calculation

To ensure 120 evaluable participants (Section 3.2.1) and accounting for a 10% attrition rate, approximately 136 subjects will be enrolled for the study. Note that the sample size for this exploratory study is not determined by statistical power considerations, but is considered adequate for the preliminary assessment of the study's objectives. To have an adequate efficacy profile of the intervention with CX-4945 in SARS-CoV-2 and influenza virus infection, the minimum evaluable size per arm in each study domain will be 20 participants.

7.2. Datasets Analyzed

7.2.1. Intent-to-Treat (ITT) Population

The ITT population is defined as all randomized subjects who receive at least one dose of CX-4945 or placebo. This population will be used as the primary analysis population for efficacy endpoints and the analysis population for baseline data, safety and exploratory endpoints.

7.2.2. Per-Protocol (PP) Population

The PP population is defined as the set of subjects who meet the ITT population and below requirements:

- Receive 80 – 120% of 10 doses of the IP during Days 1 – 6 or die before Day 6
- Not associated with any major protocol violations that have impact on efficacy evaluation

This population will be identified before the database lock and will be used as the supportive analysis population for efficacy endpoints and AE.

7.2.3. Modified Per-Protocol (mPP) Population

The mPP population is defined as the set of subjects who meet the ITT population and below requirements:

- Receive 80 – 120% of 10 doses of the IP during Days 1 – 6 or die before Day 6
- Complete the required visits by Visit 4 or die before Visit 4
- Not associated with any major protocol violations that have impact on efficacy evaluation by Visit 4

This population will be identified before the database lock and will be used as the supportive analysis population for efficacy endpoints.

7.3. General Consideration

Statistical analyses will be performed using SAS® for Windows, version 9.4 or later. All available data will be displayed via subject data listings, and summarized for each evaluation time point as appropriate by study domain (including domain-pooled) and study arm. The categorical data will be summarized with the number of subjects and percentage. Continuous data will be summarized by descriptive statistics (i.e., number of subjects, mean, standard deviation, minimum, maximum, and median). For by visit (by Day) analyses, the acceptable window for each visit will be defined in the Statistical Analysis Plan (SAP).

In general, categorical data will be analyzed by using Logistic regression (on efficacy data), Fisher's exact test or Cochran-Mantel-Haenszel test stratified by domain for comparing overall treatment group difference (treatment odds ratio for Logistic regression). For by-domain subgroup analysis on efficacy data, categorical data will be tested by using Fisher's exact test or Chi-square test.

Continuous data will be analyzed by using analysis of variance (ANOVA) on baseline data, and by using analysis of covariance (ANCOVA) on change data for comparing overall treatment group difference. Non-parametric method shall be adapted or log-transformation may be needed for non-normally distributed data. For by-domain subgroup analysis on efficacy data, continuous data will be tested by using two-sample t test or Wilcoxon Rank-sum test.

For the ANOVA, ANCOVA model and Logistic regression, factors of treatment, domain (as appropriate), site and baseline value (for post-baseline data) and other baseline factors (for post-baseline efficacy data, to be defined in the SAP, as appropriate) will be included in the model if significant, those non-statistically significant factors except treatment will be removed from the model (alpha=0.1 for interaction, 0.05 for others). The Logistic regression result will be presented with treatment odds ratio and its 95% confidence interval (CI).

All statistical tests will be two-sided and evaluated at the 0.05 level of significance. All confidence intervals, if provided, will be the 95% CI.

The most recent value before first dose administration will be defined as the baseline value; therefore, the baseline value will be the outcome of the closest evaluation performed before or equal to the first dosing date.

7.4. Patient Disposition

The disposition of all patients who signed an ICF will be provided. The number of subjects screened, screen failed, randomized, received at least one treatment, completed, and discontinued during the

study, as well as the reasons for all discontinuations will be summarized.

7.5. Concomitant Medications/Therapies/Medical Procedures

All medications will be coded to matching Anatomic Therapeutic Classification (ATC) codes using the most recent version of the WHO Drug Dictionary. Percentage of taking prior medication and concomitant medications will be presented, respectively, by the highest ATC level.

All medical procedures including surgery will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Percentage of receiving prior medical procedures and concomitant medical procedures will be presented, respectively, by the system organ class and preferred term.

All coding terms will be included in the subject data listing.

7.6. Demographic and Other Baseline Characteristics

Demographics and baseline characteristics including medical history, prior and concomitant medications/therapies and treatment exposure up to Day 6 and total treatment exposure will be summarized using appropriate statistics mentioned in section 7.3.

7.7. Efficacy Evaluation

7.7.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of subjects with the event of requiring hospitalization, emergency room visits, or resulting in death due to progression of CAP related to SARS-CoV-2 or influenza. For subjects terminated the study that event observation stopped before Day 29 and no event is observed, the subjects will be counted as 'Treatment Fail'.

The primary endpoint will be summarized in number of subjects and percentage with corresponding Clopper-Pearson exact 95% CI, and will be analyzed by using Logistic regression. Fisher's exact test or Cochran-Mantel-Haenszel test will be applied if Logistic regression is not applicable. In addition, 95% CI of treatment difference in event rate will be presented in normal approximation. Event rate including Treatment Fail rate will be tested additionally for sensitivity analysis defined in SAP.

7.7.2. Analysis of Secondary Efficacy Endpoints

The percentage of subjects with all cause hospitalization, emergency room visit or death during study period

This endpoint will be analyzed in the same way as on primary endpoint.

The percentage of subjects with improved pulmonary X-ray findings for pneumonia, relative to baseline or showing a return to normalcy

Pneumonia status will be tabulated descriptively by visit. Percentage of 'Improved' or 'Normal' will be presented with the corresponding Clopper-Pearson exact 95% CI, and tested by using Fisher's exact test or Cochran-Mantel-Haenszel test.

Time to symptom resolution for fever

Fever (ear temperature ≥ 38°C, base of the tongue temperature ≥ 37.5°C, or axillary temperature ≥ 37°C) status will be tabulated descriptively by visit. For subgroup of subjects with fever at baseline, time to symptom resolution for fever will be analyzed by using Log-rank test stratified by domain, and step plot of Kaplan-Meier graph will be provided. For subjects without symptom resolution for fever, censoring at (1) the last temperature measurement time point of the subject, (2) the last temperature measurement time point of all subjects, will both be derived for analysis.

Change from baseline in SpO_2/FiO_2 ratio

The SpO_2/FiO_2 ratio and changes in SpO_2/FiO_2 ratio will be summarized descriptively by visit. The change from baseline will be analyzed by using ANCOVA.

The percentage of subjects exhibiting disease progression / health improvement in health status

NIAID score and changes in NIAID score will be tabulated descriptively by visit. For protocol version 1.0, 6-Point Ordinal Scale collected for subjects of Influenza Virus domain will be converted to corresponding NIAID score using table below and combined with NIAID score for analyses.

6-point Score	6-point Ordinal Scale Description	NIAID 8-point Score	NIAID 8-point Description
1	Death	8	Death
2	In the intensive care unit (ICU) *Plus condition: with invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)*	7	Hospitalized with invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
2	In the intensive care unit (ICU) *Plus condition: with non-invasive ventilation or high flow oxygen supplementation*	6	Hospitalized with need of non-invasive ventilation or high flow oxygen supplementation
2	In the intensive care unit (ICU) *Plus condition: with supplemental oxygen*	5	Hospitalized with requirement of supplemental oxygen
2	In the intensive care unit (ICU) *Plus condition: with no supplemental oxygen, but with ongoing Standard of Care*	4	Hospitalized with no supplemental oxygen, but with ongoing medical care
3	Non-ICU hospitalization, requiring supplemental oxygen *Plus condition: with invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)*	7	Hospitalized with invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)

6-point Score	6-point Ordinal Scale Description	NIAID 8-point Score	NIAID 8-point Description
3	Non-ICU hospitalization, requiring supplemental oxygen *Plus condition: with non-invasive ventilation or high flow oxygen supplementation*	6	Hospitalized with need of non-invasive ventilation or high flow oxygen supplementation
3	Non-ICU hospitalization, requiring supplemental oxygen *Plus condition: with supplemental oxygen*	5	Hospitalized with requirement of supplemental oxygen
4	Non-ICU hospitalization, not requiring supplemental oxygen *Plus condition: with ongoing Standard of Care*	4	Hospitalized with no supplemental oxygen, but with ongoing medical care
4	Non-ICU hospitalization, not requiring supplemental oxygen *Plus condition: without no ongoing Standard of Care*	3	Hospitalized with no supplemental oxygen, and no ongoing medical care
5	Not hospitalized, but unable to resume normal activities	2	Not hospitalized - limitation of activities or home oxygen, or both
6	Not hospitalized with full resumption of normal activities	1	Not hospitalized with no limitation of activities

The percentage of subjects with increasing NIAID score (exhibiting disease progression) and with decreasing NIAID score (exhibiting health improvement) will be presented with the corresponding Clopper-Pearson exact 95% CI, and tested by using Fisher's exact test or Cochran-Mantel-Haenszel test, respectively.

The percentage of subjects with a negative RT-PCR result for the SARS-CoV-2 (only for SARS-CoV-2 domain) or the influenza virus (only for influenza virus domain) on Day 7

The percentage of subjects with RT-PCR negative results will be tested between treatments by using Chi-square test or Fisher's Exact test.

Change from baseline in viral load in nasal secretions by RT-PCR (only for SARS-CoV-2 domain)

The viral load and changes in viral load in nasal secretions by RT-PCR will be summarized descriptively by visit. The change from baseline will be analyzed by using ANCOVA.

Change from baseline in Ct values (only for SARS-CoV-2 domain)

The Ct values and changes in Ct values will be summarized descriptively by visit. The change from baseline will be analyzed by ANCOVA.

7.7.3. Analysis of Exploratory Endpoint

The percentage of subjects achieving normalized [redacted] levels on Day 7

Clinical Relevance ("Normal", "Abnormal, non-clinical significant (NCS)" or "Abnormal, clinical

significant (CS)") of [redacted] and its transition from baseline will be tabulated descriptively by visit.

For subgroup of subjects with baseline [redacted] levels exceed ULN, Clinical Relevance analyses will be performed additionally, and the percentage of subjects achieving normalized [redacted] levels on Day 7 will be presented with corresponding Clopper-Pearson exact 95% CI, and tested by using Fisher's exact test or Cochran-Mantel-Haenszel test.

Change from baseline in [redacted]

The values and changes in these tests will be summarized descriptively by visit. The change from baseline will be analyzed by using ANCOVA.

Note (a): According to the site labs' policy, the [redacted] or its alternative, the [redacted] test, will be conducted in the local site labs. To ensure consistency, each site lab should perform the same test [redacted] throughout the study.

Note (b): If the flow cytometry analyses for [redacted] are optional at the local site lab.

Changes from baseline in serum cytokine levels: Cytokines to be quantified; [redacted]

The values and changes in these tests will be summarized descriptively by visit. The change from baseline will be analyzed by using ANCOVA.

7.8. Safety Evaluation

All safety assessments, including TEAEs, physical examination, laboratory tests, vital signs, and electrocardiogram results, where indicated, will be presented using descriptive statistics.

7.8.1. Treatment-emergent Adverse Events (TEAEs)

This analysis applies to all treatment-emergent adverse events occurring during the study, recorded in AE eCRF. AEs occurring during the study will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to IP, will be summarized according to system organ class and preferred term within system organ class. When an adverse event occurs more than once for a subject, the maximal severity to the IP will be counted.

An overview of TEAEs will be presented with number and percentage. Separate summaries will be produced for the following categories, such as TEAEs, SAEs, Treatment-Related TEAEs, TEAEs resulting in discontinuation of study treatment and TEAEs leading to death will be presented. All coding terms will be included in the subject data listing.

7.8.2. Physical Examination

All physical examination findings will be listed. Physical abnormalities will be tabulated descriptively by visit.

7.8.3. Laboratory Tests

For continuous data, the values and changes will be summarized descriptively by visit. The change from baseline will be analyzed by using ANCOVA.

For categorical data, the values and transition from baseline will be tabulated descriptively by visit. The transition from baseline will be tested by using Fisher's exact test or Cochran-Mantel-Haenszel test.

Clinical Relevance ("Normal", "Abnormal, non-clinical significant (NCS)" or "Abnormal, clinical significant (CS)") and its transition from baseline will be tabulated descriptively.

7.8.4. Vital Signs

The values and changes in vital signs will be summarized descriptively by visit. The change from baseline will be analyzed by using ANCOVA.

7.8.5. ECG

For overall interpretation, the by visit result and its transition from baseline will be tabulated descriptively by visit. The transition from baseline will be tested by using Fisher's exact test or Cochran-Mantel-Haenszel test.

For continuous data, the values and changes will be summarized descriptively by visit. The change from baseline will be analyzed by using ANCOVA.

7.9. Handling of Missing Data

All available data will be displayed and utilized in data analysis. For by-visit efficacy endpoints, ITT analyses applying LOCF (Last Observation Carry Forward) data imputation will be performed additionally as a sensitivity analysis. Refer to **Section 7.7.1 ~ 7.7.2** for other missing data estimations.

8. DATA MANAGEMENT

8.1. Data Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented on the data entry system and data QC checks that will be run on the database will be generated. Any data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical study is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., Good Laboratory Practices [GLP], Good Manufacturing Practices [GMP]).

The investigational site will provide direct access to all study-related source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

8.2. Data Collection and Management Responsibilities

Under the supervision of the site investigator, it is the responsibility of the clinical trial staff at the site to maintain the data collection. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data collection is via Electronic Case Report Form (eCRF) completed by site staff and an electronic Patient Reported Outcome (ePRO) web-based portal by participants. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the CRF/eCRF derived from source documents should be consistent with the data recorded on the source documents. Study documents should be retained for a period complying with regulations and guidelines applicable to clinical studies of the local countries. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

Clinical data (including AEs and concomitant medications) and clinical laboratory data will be entered into data capture system, a regulatory authorities compliant data capture system provided by the responsible CRO. The data system includes password protection and internal quality checks, such as automatic range

checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be recorded/entered directly from the source documents.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

9.1. Study Monitoring

Before a study site can enter a patient into the study, a representative of the sponsor will assess the study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities regarding protocol adherence, and the responsibilities of the sponsor or sponsor's designee. This will be documented in a separate agreement between the sponsor and the investigator and/or applicable institution.

During the study, the sponsor or sponsor's designee will have regular contact with the study site for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol and International Council for Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines, that data are being accurately recorded in the CRFs, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records and/or certified copies for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the sponsor
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the sponsor, and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC

The sponsor or sponsor's designee will be available between visits if the investigator(s) or other staff needs information or advice.

9.2. Audits and Inspections

Sponsor or sponsor's designee or a designated organization, as well as regulatory authorities and IRBs/IECs must be permitted to inspect all study-related documents and other materials at the study

site, including the Investigator Site File, the completed CRFs, the IP, and the patients' original medical records/files and/or certified copies. The clinical study protocol, each step of the data capture procedure, and the handling of the data, including the final clinical study report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

The purpose of a sponsor audit or regulatory inspection is to systematically and independently examine study-related activities and documents to determine whether these activities will be conducted, and data will be recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines, and any applicable regulatory requirements. The investigator must contact the sponsor immediately if contacted by a regulatory agency about an inspection.

9.3. Institutional Review Board/Independent Ethics Committee

Prior to the commencement of the study at a given study site, the clinical study protocol will be submitted together with its associated documents (e.g., ICF, patient information sheet, IB, etc.) to the responsible IRB/IEC for its favorable opinion/approval. The written favorable opinion/approval of the IRB/IEC will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File at the sponsor or sponsor's designee.

The study must not start at a study site before the sponsor has obtained written confirmation of favorable opinion/approval from the concerned IRB/IEC. The IRB/IEC will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval will be given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the study, the clinical study protocol version and the patient information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical study will also be submitted to the concerned IRB/IEC, before implementation in case of substantial changes. Relevant safety information will be submitted to the IRB/IEC during the study in accordance with national regulations and requirements.

All IRB/IEC approvals and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

10. ETHICAL AND LEGAL ASPECTS

10.1. Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with sponsor/CRO standard operating procedures. These are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 2016.
2. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh, 2000, Washington 2002, Tokyo 2004, Seoul 2008, Fortaleza 2013).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

10.2. Delegation of Investigator Responsibilities

Responsibilities of the investigators conducting the study in addition to those stated before are enumerated below:

- Obtain Institutional Review Board (IRB) approval to conduct the clinical study.
- Provide the sponsor with written documentation that the study protocol, any protocol amendments, and the informed consent form have received IRB approval.
- Provide the sponsor with a list of IRB members, including their affiliations and qualifications. As an alternative, a General Assurance number (as assigned by the Department of Health and Human Services) fulfills this requirement.
- Report to the IRB as required. The IRB must assume continued responsibility for the study and review the research on an annual basis.
- Maintain a file of all communications with the IRB on issues related to the clinical trial.
- Conduct the study according to the protocol, ICH - GCP guidelines, and in accordance with the Declaration of Helsinki.

10.3. Subject Information and Informed Consent

Written informed consent must be obtained from all subjects prior to study participation. The informed consent form documents the information the investigator provides to the subject and the subject's agreement to participate. The investigator will fully explain the nature of the study, along with the

aims, methods, anticipated benefits, potential hazards, and discomfort that participation might entail. The informed consent must be signed and dated by each subject or legal representative before entering the study and prior to the performance of any study specific procedures.

Study site must provide the sponsor (or designee) with a copy of the informed consent approved by that site's Institutional Review Board (IRB), or Ethics Committee (EC). The subject or the subject's legally authorized representative must sign the informed consent form. The original signed consent form will be retained in the subject's study records, and a copy will be provided to the subject. The sponsor will assure that each informed consent meets the basic elements of informed consent.

10.4. Subject Rights and Confidentiality

10.4.1. Subject confidentiality

The trial staff will ensure that the subjects' anonymity is maintained. The subjects will be identified only by initials and a subject's ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorized personnel. The study will comply with the local regulation for protecting personal data stored on computers or in an organized paper filing system which requires data to be anonymized as soon as it is practical to do so.

10.4.2. Study discontinuation

The study may be discontinued at any time by the IRB, FDA/TFDA, or other government agencies as part of their duties to ensure that research subjects are protected.

10.5. Protocol Amendments

The investigator is responsible for properly notifying the sponsor of protocol changes or revisions. The investigators without prior written authorization from the sponsor may make no changes to this protocol.

10.6. Approval of the Study Protocol and Amendments

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the independent ethics committee (IEC)/institutional review board (IRB) with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities, in accordance with local legal requirements.

The IP can only be supplied to the investigator after the sponsor has received documentation on all ethical and legal requirements for starting the study. This documentation must also include a list of the members of the IEC/IRB and their occupations and qualifications. If the IEC/IRB will not disclose the names of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. Formal approval by the IEC/IRB should preferably mention the study title, study code, study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision is made and must be officially signed by a committee member.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IEC/IRB and, if applicable, the authorities must be informed of all subsequent protocol amendments, in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communication with the IEC/IRB and, if applicable, between a coordinating investigator and the IEC/IRB. This also applies to any communication between the investigator (or the coordinating investigator, if applicable) and the authorities.

10.7. Publication policy

The sponsor will not suppress or veto publications, but maintains the right to delay publication to ensure against inadvertent disclosure of confidential information or unprotected inventions. Investigators will inform the sponsor in advance of any plans to publish or present data from the study and provide the sponsor an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by investigators or their representatives will require pre-submission review by the sponsor.

Further details regarding the publication of Study results may be described in a separate agreement between the Sponsor and the Investigator and/or applicable institution.

Protocol Amendment History

Version	Date	Summary of Change	Rationale
1.0	11OCT2023	NA	Initial version
2.0	05FEB2024	- Revise the primary endpoint - Revise the secondary endpoints - Revise the exploratory endpoints - Revise the inclusion and exclusion criteria - Revise discontinuation of study Intervention - Clarify the concomitant therapy - Clarify Dosage and Administration - Add treatment compliance definition - Revise the period of Visit 1/Screening Visit - Revise the schedule of activity - Revise the subject recording platform to ePRO - Revise the study assessments - Revise AE and SAE definition and reporting - Add pregnancy reporting - Revise statistical methods - Update the abbreviation list	Per Sponsor request
3.0	16AUG2024	- Add the flow cytometry analyses for CD3 and CD4 - Revise the SOA footnote # 1 and #15 based on NtF No. NTF-C4-011-005 - Clarify the mPP population definition based on NtF No. NTF-C4-011-011 - Add the treatment compliance definition in Section 4.6 - Revise the SOA footnote #4 based on NtF No. NTF-C4-011-003 - Clarify the [redacted] tests based on NtF No. NTF-C4-011-006	Per Sponsor's requests

Version	Date	Summary of Change	Rationale
		- Revise the exploratory endpoints based on NtF No. NTF-C4-011-008 - Clarify the hospitalization definition in Sections 5.2.4.1 and 5.2.5.6 based on NtF No. NTF-C4-011-009 - Revise the PP population applied to the safety population - Revise 80 – 120% of 10 doses of the IP for the PP and mPP populations - Add the SOA footnote # 12 for PR-PCR performed in subjects who are early termination - Add the SOA footnote # 18 for one dispensation - Clarify the central or local site lab for performing RT-PCR tests - Update the abbreviation list - Revised some typos	

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