Statistical Analysis Plan

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)**
Sponsor:	**Senhwa Biosciences, Inc.**
SAP Version:	**1.0, 25-JUN-2025**
Protocol Version:	**3.0, 16-AUG-2024**

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1 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
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)
Secondary	
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 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.

Objectives	Endpoints
	(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	
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 C-reactive protein [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)

2 STUDY DESIGN

2.1 OVERALL 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

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.

2.2 RANDOMIZATION AND BLINDING

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.

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.

2.3 SAMPLE SIZE DETERMINATION

To ensure 120 evaluable participants 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.

2.4 STUDY DISCONTINUATION

Due to the reasons below, sponsor decided to stop the study early.

Insufficient Differentiation of Primary Endpoint for Unmet Medical Needs:

Based on current observations, the clinical necessity and anticipated benefits for the unmet medical needs of the target patient population have not demonstrated sufficient differentiation. Continuing enrollment may not achieve the core objectives of the study.

Recruitment Difficulties Due to the End of Influenza Season:

The influenza season is nearing its end, resulting in a substantial decrease in the number of eligible patients. Consequently, recruitment rates have significantly fallen below expectations. Considering timing and resource allocation, it has been decided to terminate enrollment early.

2.5 PROTOCOL AMENDMENTS

The initial protocol applied version is 1.0, 11-OCT-2023, and the current protocol version is 3.0, 16-AUG-2024. The first subject was enrolled on 20-MAR-2024, and the last subject was dismissed on 22-APR-2025.

Amendments relevant to important statistical-related changes are summarized in table below, which will be considered in Table/Figure/Listing programming based on the latest version of protocol.

Version Changed	Before	After
1.0→2.0	**Primary endpoint** • The percentage of subjects requiring hospitalization, **including** emergency room visits, due to progression of CAP related to SARS-CoV-2 or influenza. (Time Frame: Day 1 to Day 29)	**Primary endpoint** • 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)
1.0→2.0	**Secondary objectives** • To evaluate the effect of intervention with Silmitasertib (CX-4945) in addition to SOC, compared with placebo plus SOC, **in** reducing viral **load**	**Secondary objectives** • To evaluate the effect of intervention with Silmitasertib (CX-4945) in addition to SOC, compared with placebo plus SOC, **on** reducing viral **presence**
1.0→2.0	**Secondary endpoint** • The percentage of subjects with all cause hospitalization 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: **Day 1** to Day **5**, 15, and 29)	**Secondary endpoint** • 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)

Version Changed	Before	After
	• Time to symptom resolution for fever The symptom resolution for fever will be defined as body temperature of < 38°C. **(Time Frame: Day 1 to Day 5)** • Change from baseline in SpO_2/FiO_2 ratio (Time Frame: Day 1 to Day **5**, 15, and 29) • The percentage of subjects exhibiting disease progression in health status **(SARS-CoV-2 domain only)** Disease progression is defined as **a change in subject health status from item 1 to items 2-8, or from item 2 to items 3-8, evaluated using** the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale. (Time Frame: Day 1 to Day **5**, 15, and 29) • The percentage of subjects exhibiting **disease** improvement in health status **(SARS-CoV-2 domain only)** Health improvement is defined as **a change in subject health status from item 2 to item 1, evaluated using** the NIAID 8-point ordinal scale. (Time Frame: Day 1 to Day **5**, 15, and 29) • **The percentage of subjects exhibiting disease progression in health status (Influenza virus domain only)** **Disease progression is defined as a change in subject health status from item 6 to items 5-1, or from item 5 to items 4-1, evaluated using a 6-point ordinal scale.** **(Time Frame: Day 1 to Day 5, 15, and 29)** • **The percentage of subjects exhibiting disease improvement in health status (Influenza virus domain only)** **Health improvement is defined as a change in subject health status from item 5 to item 6, evaluated using a 6-point ordinal scale.** **(Time Frame: Day 1 to Day 5, 15, and 29)** • Change from baseline in viral load in nasal secretions by **qRT**-PCR. (only for SARS-CoV-2 domain) (Time Frame: Day 1 and Day **5**) • **Time to FilmArray confirmed resolution of viral infection** **The resolution of viral infection is defined as negative results in FilmArray.** **(Time Frame: Day 1 and Day 5)** • Change from baseline in Ct values (only for SARS-CoV-2 domain) (Time Frame: Day 1 **and** Day **5**) • 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)	• 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 SpO2/FiO2 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) • **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**) • 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)

Version Changed	Before	After
	• Electrocardiogram (ECG) results (Time Frame: **Day 1** to Day 29)	
1.0➔2.0	**Exploratory endpoint** • The percentage of subjects achieving normalized [redacted] levels **at** Day **5** (Time Frame: Day **5**) • Change from baseline in [redacted] (Time Frame: Day 1 to Day **5**, 15, and 29) [redacted] Changes from baseline in serum cytokine levels: [redacted] (Time Frame: Day 1 to Day **5**, 15, and 29)	**Exploratory endpoint** • The percentage of subjects achieving normalized [redacted] levels **on** Day **7** **This assessment will only be conducted in subjects whose [redacted] levels exceed the upper limit of normal (ULN) at Visit 2.** (Time Frame: Day 7) [redacted] Change from baseline in [redacted] (Time Frame: Day 1 to Day **7**, 15, and 29) • Changes from baseline in serum cytokine levels: Cytokines to be quantified; [redacted] (Time Frame: Day 1 to Day **7**, 15, and 29)
1.0➔2.0	**Inclusion Criteria** 1. Not currently hospitalized. 2. Males or **non-pregnant** 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. 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 **by FilmArray; if FilmArray is not available, a positive test can also be** confirmed by **a** rapid diagnostic test **or molecular diagnostic assay, using a nasopharyngeal specimen** 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 9. The participant (or legal representative) agrees to adhere to study protocols and has signed the IRB-approved Informed Consent Form (ICF) 10. With at least two of the risk factors listed below:	**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**

Version Changed	Before	After
	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.	- **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
1.0→2.0	**7.2.1 Intent-to-Treat (ITT) Population** The ITT population is defined as all randomized subjects. This population will be used as the primary analysis population for efficacy endpoints.	**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.**
1.0→2.0	**7.2.2 Per-Protocol (PP) Population** The PP population is defined as the set of subjects who meet the ITT population requirements and are not associated with any major protocol violations. This population will be identified before the database lock**. This population** will be used as the supportive analysis population for efficacy 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 at least 80% of 10 doses of investigational product 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.
1.0→2.0	**7.2.3 Safety Population** **The Safety population is defined as any subjects receiving at least one dose of CX-4945 or standard of care treatment after randomization. This population is for safety evaluation in analysis.**	**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 at least 80% of 10 doses of investigational product during Days 1 – 6 or die before Day 6** • **Complete the required visits by Visit 4 or die before Visit 4**

Version Changed	Before	After
		• **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.**
1.0→2.0	**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 **tabulated** by study domain and study arm. The categorical data will be summarized with the number of subjects and percentage **with the corresponding 95% confidence interval.** Continuous data will be summarized by descriptive statistics (i.e. number of subjects, mean, standard deviation, minimum, maximum, and median). In general, **discrete** data will be analyzed by Fisher's exact test for comparing group difference in each domain; continuous data will be analyzed by two sample t test. 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% **confidence intervals**. 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.	**7.3 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).**

Version Changed	Before	After
		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.
1.0→2.0	**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 **by treatment group. Disposition and reason for study discontinuation will also be provided as a by-subject listing.**	**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.
1.0→2.0	**7.5 Concomitant Medications/Therapies** **Concomitant medications/therapies will be summarized separately for the Safety population. All prior and concomitant** medications recorded in the case report form will be coded to matching Anatomic Therapeutic Classification (ATC) codes using the most recent version of the WHO Drug Dictionary. **The number and** percentage of participants with concomitant medications will be presented by **ATC level 1 and ATC level 2, study domain, and study arm. Individual participant listings will be presented for all concomitant medications/therapies recorded in the database.**	**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.**
1.0→2.0	**7.6 Demographic and Other Baseline Characteristics** Demographics and baseline characteristics including medical history, prior and concomitant medications/therapies will be summarized **by study domain and study arm** using appropriate descriptive statistics. **No formal testing of demographic or baseline characteristics will be performed.**	**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.**
1.0→2.0	**7.7.1 Analysis of Primary Efficacy Endpoint**	**7.7.1 Analysis of Primary Efficacy Endpoint**

Version Changed	Before	After
	The primary efficacy endpoint is the percentage of subjects requiring hospitalization, **including** emergency room visits, due to progression of CAP related to SARS-CoV-2 or influenza. that will be summarized by number of subjects and percentage with corresponding Clopper-Pearson exact 95% CI. Fisher's exact test or Chi-square test is performed for comparison of study arms in each domain as appropriate.	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.**
1.0➔2.0	**7.7.2 Analysis of Secondary Efficacy Endpoints** • The percentage of subjects with all cause hospitalization during study period **The percentage of subjects with all cause hospitalization during study period will be summarized by number of subjects and percentage with corresponding Clopper-Pearson exact 95% CI. Fisher's exact test or Chi-square test is performed for comparison of study arms in each domain as appropriate.** • The percentage of subjects with improved pulmonary X-ray findings for pneumonia, relative to baseline or showing a return to normalcy **The percentage of subjects with improved pulmonary X-ray findings for pneumonia, relative to baseline or showing a return to normalcy** will be **summarized** by **number of subjects and percentage** with corresponding Clopper-Pearson exact 95% CI. Fisher's exact test or **Chi-square** test **is performed for comparison of study arms in each domain as appropriate**. • Time to symptom resolution for fever Time to symptom resolution for fever will be analyzed using the Kaplan-Meier method, and survival curves will be provided, if applicable. Log-rank test will be used to evaluate difference between study arms in each domain. • 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 **presented** by descriptive statistics. The change from baseline **in SpO2/FiO2 ratio** will be analyzed by **analysis of covariance** (ANCOVA) **with the baseline value and study arm as covariates.**	**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 SpO2/FiO2 ratio The SpO2/FiO2 ratio and changes in SpO2/FiO2 ratio will be **summarized descriptively** by visit. The change from baseline will be analyzed by using **ANCOVA**.

Version Changed	Before	After
	• The percentage of subjects exhibiting disease progression in health status (SARS-CoV-2 domain only) The percentage of subjects exhibiting disease progression in health status will be summarized with number of subjects and percentage. Fisher's exact test or Chi-square test is performed for comparison of study arms as appropriate. • The percentage of subjects exhibiting disease improvement in health status (SARS-CoV-2 domain only) The percentage of subjects exhibiting disease improvement in health status will be summarized with number of subjects and percentage. Fisher's exact test or Chi-square test is performed for comparison of study arms as appropriate. • Change from baseline in viral load in nasal secretions by qRT-PCR (only for SARS-CoV-2 domain) The viral load **in nasal secretions by qRT-PCR** and changes in viral load in nasal secretions by qRT-PCR will be presented by descriptive statistics. The change from baseline **in viral load** in nasal secretions by qRT-PCR will be analyzed by ANCOVA with the baseline value and study arm as covariates. • **Time to FilmArray confirmed resolution of viral infection** **Time to FilmArray confirmed resolution of viral infection will be analyzed using the Kaplan-Meier method, and survival curves will be provided, if applicable. Log-rank test will be used to evaluate difference between study arms in each domain.** • Change from baseline in Ct values (only for SARS-CoV-2 domain) The Ct values and changes in Ct values will be summarized descriptively. The change from baseline **in Ct** values will be analyzed by ANCOVA **with the baseline value and study arm as covariates.**	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.** … 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.
1.0➔2.0	**7.7.3 Analysis of Exploratory Endpoint** • The percentage of subjects achieving normalized [redacted] levels **at** Day **5** The percentage of subjects achieving normalized [redacted] levels **at** Day **5** will be summarized by number of subjects and percentage with corresponding Clopper-Pearson exact 95% CI. Fisher's exact test or **Chi-square** test **is performed for comparison of study arms in each domain as appropriate.** • Change from baseline in [redacted]	**7.7.3 Analysis of Exploratory Endpoint** The percentage of subjects achieving normalized CRP 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.**

Version Changed	Before	After
	The [redacted] will be summarized descriptively. **The change from baseline in** [redacted] will be analyzed by ANCOVA **with the baseline value and study arm as covariates.** [redacted] Changes from baseline in serum cytokine levels: Cytokines to be quantified; [redacted] The **serum cytokine levels** and changes in serum cytokine levels will be summarized descriptively. The change from baseline **in serum cytokine levels** will be analyzed by ANCOVA **with the baseline value and study arm as covariates.**	**For subgroup of subjects with baseline** [redacted] **levels exceed ULN, Clinical Relevance analyses will be performed additionally, and the** percentage of subjects achieving normalized CRP 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. 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.
1.0→2.0	**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 **study groups**, 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 **study groups** 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, **Related** TEAEs, TEAEs resulting in discontinuation of study treatment and TEAEs leading to death will be presented. **Data listings of all adverse events will be provided by subjects.**	**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.**
1.0→2.0	**7.8.2. Physical Examination** All physical examination findings will be listed **and summarized by time points and study arms. Shift table will be also presented, if appropriate.**	**7.8.2. Physical Examination** All physical examination findings will be listed. **Physical abnormalities will be tabulated descriptively by visit.**
1.0→2.0	**7.8.3. Laboratory Tests**	**7.8.3. Laboratory Tests**

Version Changed	Before	After
	Laboratory test parameters (hematology and biochemistry) and the change from baseline will be summarized with descriptive statistics by study arms and time points. Shift table for laboratory data will be shown by visit using categorization of laboratory according to laboratory's normal reference range.	**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.**
1.0→2.0	**7.8.4. Vital Signs** All vital sign findings will be listed, and descriptive statistics also be summarized by time points and study arms. Change from baseline will also be summarized using descriptive statistics as appropriate.	**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.**
1.0→2.0	**7.8.5. ECG** All ECG values will be listed. ECG measurements will also be summarized and presented by study arms and time points in study domains.	**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.**
1.0→2.0	**7.9. Handling of Missing Data** All available data will be displayed and utilized in data analysis. For categorical efficacy endpoints, no imputation will be considered for missing values. For continuous efficacy endpoints, LOCF (Last Observation Carry Forward) data will be presented for missing values as a sensitivity analysis. If the last observation is baseline value, imputation will not be carry out.	**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.**

Version Changed	Before	After
2.0→3.0	**Exploratory Endpoints Endpoints** • The percentage of subjects achieving normalized [redacted] levels on Day 7 This **assessment** will only be conducted in subjects whose [redacted] levels exceed the upper limit of normal (ULN) at Visit 2. (Time Frame: Day 7) [redacted] Change from baseline in [redacted] (Time Frame: Day 1 to Day 7, 15, and 29)	**Exploratory Endpoints Endpoints** • 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 can be omitted.**
2.0→3.0	**Per-Protocol (PP) Population** The PP population is defined as the set of subjects who meet the ITT population and below requirements: • Receive **at least 80%** of 10 doses of **investigational product** 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.	**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**.
2.0→3.0	**Modified Per-Protocol (PP) Population** The mPP population is defined as the set of subjects who meet the ITT population and below requirements: • Receive **at least 80%** of 10 doses of **investigational product** 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.	**Modified Per-Protocol (PP) 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.

3 STATISTICAL CONSIDERATIONS

3.1 ANALYSIS POPULATION

The following populations will be introduced for statistical analysis.

Analysis population	Description
Intent-to-Treat (ITT) Population	All randomized subjects who receive at least one dose of CX-4945 or placebo
Per-Protocol (PP) Population	• The set of subjects who meet the ITT population • 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
Modified Per-Protocol (mPP) Population =Evaluable subjects	• The set of subjects who meet the ITT population • 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

ITT population will be used as the primary analysis population for efficacy endpoints and the analysis population for baseline data, safety and exploratory endpoints. PP population will also be applied on AE analysis. PP and mPP populations will be used as the supportive analysis population for efficacy endpoints.

All analyses will be performed on actual treatment taken unless otherwise specified. For PP and mPP populations, all inclusion and exclusion criteria should be fulfilled as applied in the latest version.

3.2 STATISTICAL ANALYSES

3.2.1 STATISTICAL HYPOTHESES

There is no statistical testing in this study.

3.2.2 GENERAL APPROACH

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).

In general, categorical data will be analyzed by using Fisher's exact test or Cochran-Mantel-Haenszel test stratified by domain for comparing overall treatment group difference. For by-domain subgroup analysis, 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, baseline continuous data will be tested by using two-sample t test or Wilcoxon Rank-sum test, post-treatment continuous data will be tested by using ANCOVA or Wilcoxon Rank-sum test.

For the ANOVA and ANCOVA model, factors of treatment, domain (as appropriate), site and baseline value (for post-baseline data) and other baseline factors 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).

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.

3.2.3 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. Fisher's exact test or Cochran-Mantel-Haenszel test will be applied. 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 section 3.2.9.

3.2.4 Analysis of Secondary Efficacy Endpoint

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 $\geq$ 38°C, base of the tongue temperature $\geq$ 37.5°C, or axillary temperature $\geq$ 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.

In the protocol (Section 5.2.5.2, Vital signs), it is specifies that the body temperature assessed at site on Day 1 should be baseline. Upon review of the data collected on Day 1, it was found that some body temperatures measured by subject before dosing were entered in electronic Patient Reported Outcomes (ePRO). Therefore, the definition of baseline body temperature will be revised to consider the measurement (from either ePRO or on-site) that is closest to the time before dosing on Day 1.

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 *(refer to [Instructions and Abbreviations] of Subject Data Listings Specification for NIAID 6-point Score Conversion to 8-point Score)* and combined with NIAID score for analyses.

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.

FilmArray data (Negative/Positive) obtained from Protocol v.1.0 will be integrated into and considered equivalent to the results for RT-PCR.

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.

3.2.5 Safety Analyses

Treatment-emergent Adverse Events (TEAEs)

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.

Physical Examination

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

Laboratory Tests

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

For categorical laboratory 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.

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.

ECG

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

3.2.6 Exploratory Analyses

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.

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.

3.2.7 Baseline Statistics

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 3.2.2.

3.2.8 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.

3.2.9 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.

3.2.10 Visit Adjustment

For all efficacy and safety analyses, the visit (not including unscheduled visit) out of acceptable window and the Early Termination Visit (Visit 5) of early terminated subject will be reallocated to an appropriate scheduled visit according to below acceptable visit window.

Visit Name	Visit Day	Acceptable visit window
Visit 1 (Screening)	-1 ~ 1 *(v1.0)*	NA

Visit Name	Visit Day	Acceptable visit window
	-2 ~ 1 *(else)*	
Visit 2 (Day 1)	1	NA
Visit 3 (Day 5/7)	5 ± 1 *(v1.0)* 7 ± 1 *(else)*	Day 4~10
Visit 4 (Day 15)	15 ± 2	Day 11~20
Visit 5 (Day 29)	29 ± 3	Day 21~40

3.2.11 SENSITIVITY ANALYSES

For primary efficacy endpoint and secondary points that is the percentage of subjects with all cause hospitalization, emergency room visit or death during study period, event rate including 'Treatment Fail' rate will be tested.

For time to symptom resolution for fever and 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.

For by-visit efficacy endpoints, ITT analyses applying LOCF (Last Observation Carry Forward) will be performed.

3.2.12 SUBGROUP ANALYSES

Domain includes SARS-CoV-2 Domain and Influenza Virus Domain. By-domain subgroup analysis will be performed. Other subgroup analyses which are conditioned to the test are mentioned in section 3.2.4 and 3.2.6.

3.2.13 AD HOC ANALYSIS

An ad hoc exploratory subgroup analysis will be conducted in this study. The analysis will be performed separately within the HIV and Non-HIV groups to evaluate differences in inflammatory markers and cytokine between treatment arms. Additionally, the analysis will also be performed within the Asthma and Non-Asthma groups.

3.3 STATISTICAL/ANALYTICAL ISSUES

3.3.1 ADJUSTMENTS FOR COVARIATES

Due to early termination of the study, there was a small number of subjects enrolled at most sites. In addition, there was no similar site-related properties among sites. Therefore, Site is not considered as a factor in the ANOVA and ANCOVA model; only treatment, domain (as appropriate), and baseline value (for post-baseline data) are the factors in the ANOVA and ANCOVA model.

3.3.2 HANDLING OF DROPOUTS OR MISSING DATA

For primary efficacy endpoint and secondary points that is the percentage of subjects with all cause hospitalization, emergency room visit or death during study period, the subject will be counted as 'Treatment Fail' when subject has been terminated the study and event observation has been stopped before Day 29 with no event observed.

For by-visit efficacy endpoints, ITT analyses applying LOCF (Last Observation Carry Forward) data imputation will be performed additionally as a sensitivity analysis.

3.3.3 Handling of Protocol Deviations

Protocol deviations, including operational and non-operational deviations, will be verified and logged according to SOP. Major DVs of this study, including the items below but not limited to, will be justified by the BSS upon the confirmation of sponsor. Relevant statistics are displayed in Tables 14.1.3.

- Violation of inclusion/exclusion criteria (wrong subject entry)
- Administration of prohibited therapy (medication / procedure / surgery)
- Non-compliant with the key study procedures
- Measurement/visit out of scheduled time window that may have significant impact on key efficacy / safety data
- Low treatment compliance / exposure
- Study was not withdrawn according to study withdrawal criteria

3.3.4 Interim Analysis and Data Monitoring

There is no planned interim analysis in this study.

3.3.5 Multicenter Studies

This is a multi-center study. Data from all sites will be pooled for analysis.

3.3.6 Multiple comparison/multiplicity

Not applicable.

3.3.7 Use of an "Efficacy Subset" of Subjects

In addition to ITT population, efficacy data will be analyzed in PP and mPP population.

3.3.8 Active-Control Studies Intended to Show Equivalence

Not applicable.

3.3.9 Drug Dose, Drug Concentration, and Relationships to Response

Not applicable.

3.3.10 Drug and Drug Disease Interactions

Not planned in this study.

3.3.11 By Subject Display

Individual subject data will be listed by measure and time point.

By-subject data are displayed in **Appendix 16.2**.

3.4 CHANGES FROM PROTOCOL-PLANNED ANALYSES

All the eligibility criteria will follow the latest version of study protocol. Visit Adjustment is defined in section 3.2.8.

3.4.1 STATISTICAL METHODS CHANGE

Due to early termination of the study, only 44 subjects were randomized. For both the primary and secondary endpoints, the number of events observed prior to unblinding was insufficient to support reliable estimation using logistic regression. Therefore, Logistic regression will not be applied in the analysis.

3.4.2 HANDLING OF DOMAIN IN STATISTICAL ANALYSIS

For subjects with positive FilmArray results for both SARS-CoV-2 and Influenza Virus, the domain used for statistical analyses, including but not limited to subgroup analysis and ANOVA/ANCOVA modeling, will be conducted based on their randomized domain group.

3.4.3 BY-DOMAIN SUBGROUP ANALYSIS - CONTINUOUS DATA

For by-domain subgroup analysis, baseline continuous data will be tested by using two-sample t test or Wilcoxon Rank-sum test, post-treatment continuous data will be tested by using ANCOVA or Wilcoxon Rank-sum test.

3.4.4 DEFINITION OF BASELINE TEMPERATURE

The ePRO or on-site temperature measurement may be closer to the actual time of dosing. Therefore, the baseline body temperature will be defined as the measurement from either ePRO or on-site data that is closest to the time before dosing on Day 1.

3.4.5 AD HOC ANALYSIS

An ad hoc exploratory subgroup analysis will be conducted in this study. See the details in Section 3.2.13.

3.5 STATISTICAL SOFTWARE

All statistical analyses will be conducted using SAS statistical software version 9.4 or higher.

3.6 MOCK-UP TABLES, FIGURES AND LISTING

Tables, figures and listing are presented in separate documents below:

- Statistical Analysis Plan: Mock-up Tables and Figures
- Statistical Analysis Plan: Subject Data Listings Specification

4 ABBREVIATIONS AND DEFINITIONS

Abbreviation	Term
AE	Adverse Event
ALQ	Above the Limit of Quantification
BLQ	Below the Limit of Quantification
CI	Confidence Interval
CRF	Case Report Form

Abbreviation	Term
DVs	Protocol deviations / violations
IQR	Inter-Quartile Range
TFL	Table, Figure, Subject Listing
Q3	Third Quartile
Q1	First Quartile
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedures

For protocol / CRF related abbreviations, please refer to corresponding document.

5 REVISION HISTORY

Version	Date	Author	Description of Changes
1.0	25-JUN-2025	Ariel Cheng	This is the first version