STATISTICAL ANALYSIS PLAN

Study Title

A Phase IIb, Randomized, Double-blind, Multicenter, Placebo-controlled Study Evaluating the Efficacy and Safety of CT-P27 in Subjects with Acute Uncomplicated Influenza A Infection

Protocol No./ Version

CT-P27 2.2/ V5.0

Sponsor

Celltrion, Inc.

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V3.1

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Statistical Analysis Plan

Approved by Sponsor

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Statistical Analysis Plan

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Abbreviation

Term	Definition
ADE	Antibody-Dependent Enhancement
AEs	Adverse Events
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Curve
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CS	Clinically Significant
CSR	Clinical Study Report
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOS	End-of-Study
Flu-iiQ^{TM}	Influenza Intensity and Impact Questionnaire
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
HA	Hemagglutinin
HI	Hemagglutination Inhibition
ICF	Informed Consent Form
ICH	International Council for Harmonization
IP	Investigational Product
ITT	Intent-to-Treat
ITTI	Intent-to-Treat Infected
LLoQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NA	Neuraminidase
NCS	Not Clinically Significant
PK	Pharmacokinetics
PT	Preferred Term
QoL	Quality of Life
qPCR	quantitative Polymerase Chain Reaction
SAE	Serious Adverse Event

Term	Definition
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
$TCID_{50}$	Median Tissue Culture Infected Dose
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
ULoQ	Upper Limit of Quantification
WHODD	World Health Organization Drug Dictionary

[redacted]

Statistical Analysis Plan

Contents

1. Introduction

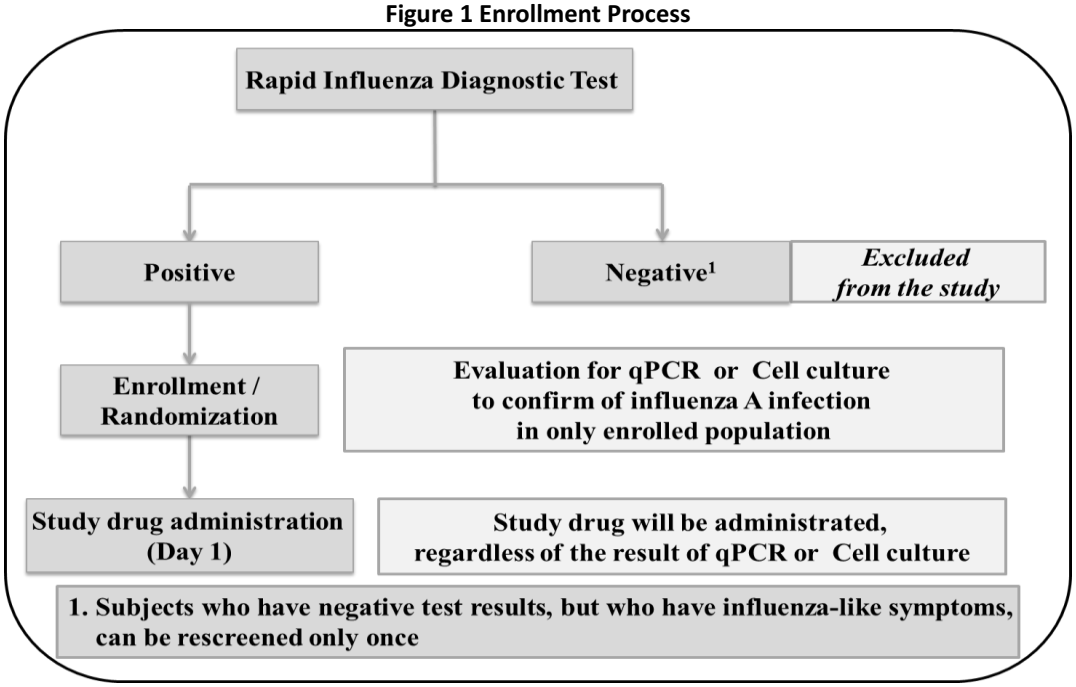
1.1 Study Design and Plan

The Statistical Analysis Plan (SAP) is based on the final study protocol CT-P27 2.2 (A Phase IIb, Randomized, Double-blind, Multicenter, Placebo-controlled Study Evaluating the Efficacy and Safety of CT-P27 in Subjects with Acute Uncomplicated Influenza A Infection) Version 5.0 dated 31 January 2018 and electronic Case Report Form (eCRF) Version 4.1 dated 28 September 2017 and covers full study analysis and data presentation. This is a phase IIb, multicenter, placebo-controlled, randomized, double-blind, parallel-arm study to evaluate the efficacy and safety of two doses of CT-P27 (45 mg/kg and 90 mg/kg) in subjects with acute uncomplicated influenza A infection. This proof-of-concept study will provide dose-ranging information for the subsequent clinical development of the drug.

No study procedures will be performed prior to informing the subject about the study and obtaining written informed consent. However, any test result which was obtained within the allowed screening period can be used as screening data for subject's convenience. It is critical that subjects receive treatment with study drug no more than 48 hours after the onset of symptoms (window of +12 hours is allowed). The time of onset of illness is defined as the earlier of either (a) the time when the body temperature was first measured as ≥ 38.0°C (≥100.4°F) or (b) the time when the subject experienced the presence of at least two symptoms that are respiratory and/or constitutional (moderate to severe in intensity). For most subjects, obtainment of the Informed Consent Form (ICF), screening for eligibility, randomization and treatment will occur on the same day. Though obtainment of the ICF may occur on the day prior to screening, randomization or treatment, it must be within 24 hours before the administration of study drug.

To be eligible for enrollment, subjects must have a positive test result for influenza A by a rapid influenza diagnostic test. At screening, nasopharyngeal swab samples will be collected for two times to be used for rapid influenza diagnostic test and virology assessment. The enrollment process is presented in Figure 1.

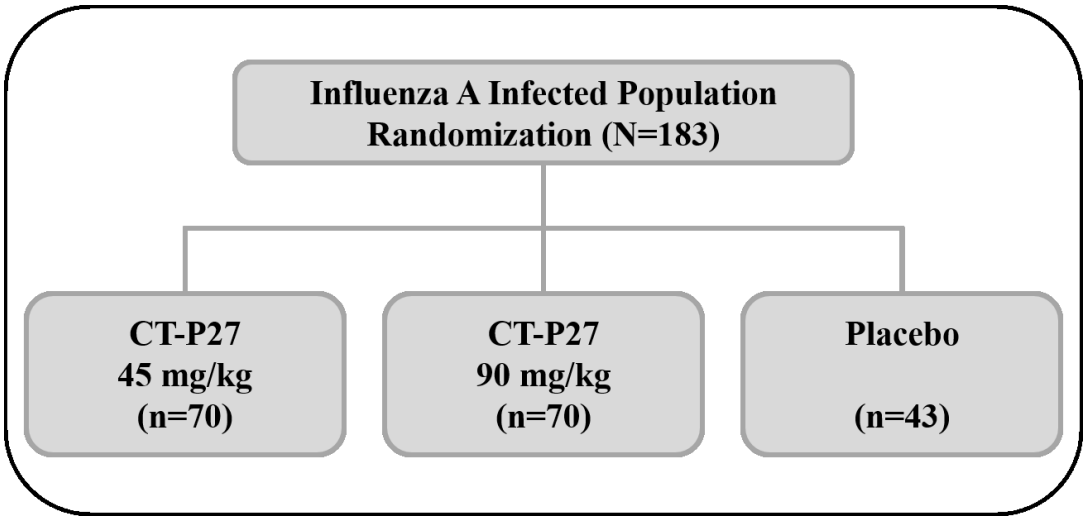
Figure 1 Enrollment Process



Approximately 183 subjects with influenza A to be enrolled in the study will be randomly assigned to 1 of 3 groups, CT-P27 45 mg/kg, CT-P27 90 mg/kg, or placebo (approximately 70 subjects per CT-P27 treatment groups and 43 subjects in placebo group). Randomization will be stratified by flu vaccination history within a year (Yes vs No) and participation in Pharmacokinetic (PK) sub-study (Yes vs No). A schematic diagram of

subject assignment is presented in Figure 2.

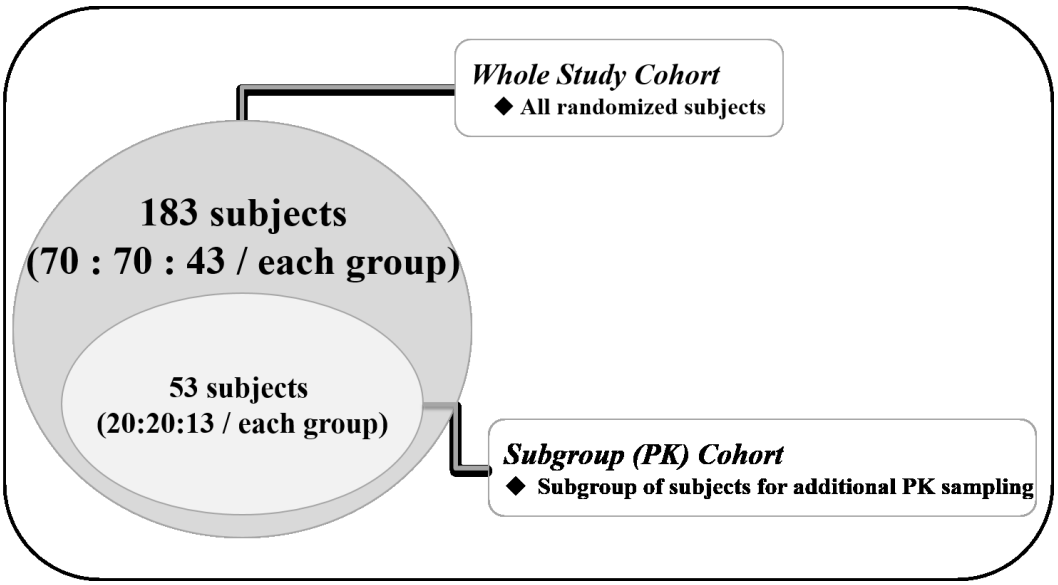
Figure 2 Schematic diagram of Subject Assignment



All enrolled subjects will be given a single dose of CT-P27 45 mg/kg, CT-P27 90 mg/kg, or placebo intravenously over 90 minutes (±15 minutes) on Day 1 and then followed by Day 110.

A PK sub-study will be performed on the subjects who signed informed consent to participate in a PK sub-study. Of total number of subjects to be enrolled, approximately 53 subjects (20 subjects per CT-P27 treatment groups and 13 subjects in placebo group) will be included in the Subgroup (PK) Cohort, and additional PK samples from the subjects in this cohort will be collected according to the schedule of assessments. A schematic diagram for the study cohorts is presented in Figure 3.

Figure 3 Schematic Diagram for the Study Cohorts



Subjects may be admitted to a hospital from Day 1 (before study drug administration) to Day 3 (after completion of the 48 hours assessments) if deemed necessary by the investigator's judgement.
The first analysis of data will occur after all subjects have completed the assessments scheduled for Day 15.

As study recruitment was conducted through 2 influenza seasons to reach the expected sample size, approximately 1-year gap has been made between the subjects who enrolled during first season (randomized before 30Apr2017) and second season (randomized from 01May2017). To include as much available data as possible in the 1st Clinical Study Report (CSR), the whole data up to Day 110/EOS visit for the first season subjects, and the data up to Day 15 for the second season subjects will be summarized in the 1st CSR. In the Follow-Up CSR, the whole data up to study close will be included and summarized.

These data will be used to determine the efficacy of treatment with CT-P27 to establish an effect size of CT-P27 in comparison to placebo based on time to resolution of influenza symptoms and fever. Information on effect size, as well as the safety and PK will be used in the selection of doses for subsequent clinical studies.

2. Objectives

2.1 Primary Objective

To evaluate efficacy as determined according to the time to resolution of respiratory and constitutional symptoms of influenza and fever

2.2 Secondary Objectives

To evaluate the additional efficacy and safety of CT-P27, including potential effects on the incidence of Antibody-Dependent Enhancement (ADE)

2.3 Exploratory Objectives

- To assess the PK of CT-P27 components (CT-P22 and CT-P23)
- To assess immunogenicity
- To assess Hemagglutination Inhibition (HI) antibody
- To assess the characterization of isolated influenza viruses

3. Endpoints

3.1 Efficacy Endpoints

Primary Efficacy Endpoint:

The primary efficacy endpoint is defined as the time from the administration of study drug to resolution of influenza symptoms and fever as recorded in the diary.

Resolution of symptoms has occurred if the following influenza symptoms recorded on the Influenza Intensity and Impact Questionnaire (Flu-iiQ™) in the diary are mild in intensity or none for at least 24 hours.

- Respiratory symptoms (cough, sore throat, and nasal congestion)
- Constitutional symptoms (headache, feeling feverish, body aches and pains, and fatigue)

Resolution of fever is defined as:

- Body temperature of <37.0℃ for at least 24 hours

Secondary Efficacy Endpoints:

- Time to resumption of normal activity as reported in Domain 2 of the Flu-iiQ™
- Time to return to normal body temperature (<37.0℃) for at least 24 hours
- Time to resolution of individual symptoms for at least 24 hours as reported in Domain 1 of the Flu-iiQ™
- Severity of symptoms as reported in Domain 1 of the Flu-iiQ™
- Viral shedding in nasopharyngeal swab samples
- Incidence of secondary complications of influenza
- Quality of Life (QoL) measures as reported in Domain 3 and Domain 4 of the Flu-iiQ™
- Physician assessment

3.2 Safety Endpoints

The following safety parameters are secondary endpoints:

- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious adverse events (TESAEs)
- Clinical laboratory analyses (hematology, biochemistry, and urinalysis laboratory tests)
- Vital sign measurements
- Immediate hypersensitivity monitoring
- Electrocardiograms (ECGs)
- Physical examination findings
- Weight assessment
- Pregnancy test
- Chest X-ray
- Evaluation of ADE throughout the entire study duration

3.3 Exploratory Endpoints

- PK profiles:
  - $AUC_{0-\infty}$: Area under the concentration-time curve in serum from time zero extrapolated to infinite time
  - AUC_{0-last}: Area under the concentration-time curve from time zero to the last quantifiable concentration
  - C_{max}: Maximum observed serum concentration
  - t_{max}: Time of maximum concentration
  - C_{last}: Last observed quantifiable concentration
  - λ_z: Apparent terminal elimination rate constant
  - $t_{1/2}$: Apparent terminal elimination half-life
  - MRT : Mean residence time
  - CL : Systemic clearance from serum after IV dosing
  - V_z : Apparent volume of distribution during the terminal elimination phase after IV dosing
- Immunogenicity analysis:
  - Anti-drug specific antibodies and neutralizing antibodies for CT-P27 component antibodies (CT-P22 and CT-P23)
- HI antibody
- Genotype and phenotype of isolated influenza virus

4. Randomization, Stratification and Blinding

Subjects will be randomly assigned to a treatment group after they provide an ICF and meet all the inclusion criteria and none of the exclusion criteria by using Interactive Web Response System (IWRS). The randomization will be stratified by flu vaccination history within a year (Yes vs No) and participation in PK sub-study (Yes vs No).

This study will be double-blinded. The study blind will not be broken except in a medical emergency (where knowledge of the investigational medicinal product administered would affect the treatment of the emergency) or regulatory requirement (e.g., for Serious Adverse Event (SAE) or death). If the blind is broken, the date, time, and reason must be recorded in the subject's eCRF and any associated AE report.

The database will be unblinded to unblind person predefined by the sponsor [redacted]. However, the study will remain blinded to the investigators and subjects until study termination.

5. General Statistical Considerations

5.1 General Analysis Considerations

The statistical analysis will be performed using [redacted]. Any deviations from the planned analysis as described in this SAP will be justified and recorded in the CSR.

The data documented and the clinical parameters measured in this study will be described using descriptive statistics (including number [n], mean, median, Standard Deviation (SD), minimum, and maximum) for continuous variables: minimum and maximum will be presented to the same number of decimal places as the raw data, mean and median will be presented to one more decimal place than the raw data, and SD will be presented to two more decimal places than the raw data. If the geometric mean is to be presented, it will be set to the same precision as the mean. However, geometric mean will not be calculated when minimum value from the data is zero. Percent Coefficient of Variation (CV%) will be presented to two decimal places. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001". If a p-value is greater than 0.999 it will be reported as ">0.999".

Categorical data will be summarized using count and percentage in each category. Percentages will be presented to one decimal place. The percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. "Not done" and "Missing" category will be included to account for cases of no assessment and missing respectively even if they are not recorded in eCRF. The denominator for all percentages will be the number of subjects within the treatment group for the population of interest, unless otherwise indicated.

All data will be displayed in listings. Unless otherwise specified, listings will be sorted by the treatment group, subject number, and assessment date or visit date, if applicable. In cases where more ordering is required, other variables will be included in the sort order as applicable.
Baseline will be the latest available measurement prior to the start of the infusion of study drug.

When summarizing End-of-Study (EOS) visit, the early termination cases are excluded from the summary for EOS visit, but will be presented in data listings. Unscheduled results will not be included in the summary tables except for determining baseline or if unscheduled results are necessary to interpret data, but they will be presented in data listings.

5.2 Determination of Sample Size

This study is designed to obtain effect sizes of 2 different CT-P27 treatment groups and placebo group based on the time from the administration of study drug to resolution of influenza symptoms and fever.
For this proof-of-concept dose-ranging study, assuming 90% of subjects are included in the eligible infected population, the total eligible sample size of 164 (63 eligible infected subjects per CT-P27 treatment groups and 38 subjects in placebo group) achieves 80% power to detect 1.8 days of reduction for the primary endpoint of time to resolution with 5% two-sided significance level and SD of 3 days using a Wilcoxon's rank-sum test.
Considering a dropout rate of 10%, this study will need 183 subjects to be enrolled to achieve 164 evaluable subjects.
For an effect size of 1.5 days of reduction in time to resolution with SD of 2.9 days, the total sample size could be increased to about 250 to achieve at least 80% statistical power with 5% two-sided significance level.

5.3 Analysis Populations

ITT and ITTI populations will be analyzed according to the randomized treatment groups and safety and PK populations will be analyzed according to the actual treatment groups.

- Intent-to-Treat (ITT) Population: defined as all subjects randomized to study drug.
  All subjects will be included in the ITT as randomized even if they do not receive treatment, except

for the following situation:

Subjects who are screening failures but are randomized in the IWRS by accident and do not receive any study drug will not be included in the ITT population.

- Intent-to-Treat Infected (ITTI) Population: defined as all randomized subjects with confirmed influenza A by quantitative Polymerase Chain Reaction (qPCR) or cell culture.
- Safety Population: defined as all randomized subjects receiving any amount (full or partial dose) of study drug, except for the following situation:

  Subjects who do not receive study drug but receive normal saline solution will be included in the safety population and they will be analyzed in the placebo group.
- PK Population: defined as all randomized subjects with confirmed influenza A by qPCR or cell culture who received a complete dose of study drug, with at least one post-dose PK sample.

If infusion interruptions and/or infusion rate adjustments occur during the drug administration, the subject is still considered to have received a complete dose provided that the full calculated dose (45 mg/kg or 90 mg/kg) has been given at the end of the infusion.

The analysis populations will be used for the analyses as follows:

- ITT Population:
  - Demographic and baseline characteristics
  - Use of drugs for symptom relief
  - Secondary efficacy endpoints
- ITTI Population:
  - Demographic and baseline characteristics
  - Primary efficacy endpoint
  - Secondary efficacy endpoints
  - Genotype
  - Phenotype
- Safety Population:
  - Viral serology
  - Prior and concomitant medications
  - Study drug exposure
  - Safety endpoints
  - Immunogenicity
- PK Population:
  - Demographic and baseline characteristics
  - PK analysis
  - HI antibody

HI antibody, genotype and phenotype will be analyzed in the Follow-Up CSR only.

5.4 External Data Handling

When combining data from eCRF and that of analytical facilities such as [redacted], discrepancy will be handled as follows:

1) Recorded as collecting sample in eCRF but no corresponding results from analytical facility – listing will display only sample collection visit/date/time from eCRF;

2) No corresponding records in eCRF for results from analytical facility – listing will display only specimen collection visit/date and results from analytical facility;

3) Discrepancy in sample collection date from eCRF and analytical facility – listing will display results from analytical facility and visit/date/time from eCRF if not missing; if sample collection date/time is missing in

eCRF then use specimen collection visit/date from analytical facility.

6. Protocol Deviation

Subject data will be reviewed for major protocol deviations by a qualified clinical reviewer prior to the blinded Data Review Meeting (DRM). In the DRM, all analysis populations will be also reviewed and documented prior to unblinding the study. The protocol deviations will be classified as 7 types:

- Inclusion/Exclusion criteria & Consent procedure
- Investigational Product (IP) dosing error, IP usage error
- IP dispensing error
- Use of unauthorized treatment (e.g., prohibited drug, restricted drug)
- Visit window deviation
- Failure to perform required study procedure
- Other

Protocol deviation listing with classified type and description of deviation will be presented for the ITT population.

7. Subject Disposition

The number of subjects who are screened, randomized, and treated with study drug will be summarized in the ITT population. Reason of screening failure will be summarized overall and the number of administered subjects who have completed or discontinued study will be summarized with reason of discontinuation by treatment group and overall.

A subject will be considered to have been randomized if the subject is allocated to a randomization number as recorded on the 'Randomization Requirements' page of the eCRF. A subject will be considered to have administered treatment in the study if "Yes" was recorded for the question, 'Was the Study Drug Administration performed?' in 'Study Drug Administration' page of the eCRF. A subject will be considered to have completed the study if "Yes" was recorded for the question, 'Did the subject complete the study?' in 'End of Study' page of the eCRF. Likewise, a subject is considered to have discontinued the study if "No" was recorded for the same question. A subject will be considered to be ongoing the study if they have been randomized and no information has been yet recorded in the 'End of Study' page of the eCRF.

8. Demographics and Baseline Characteristics

Demographics and other baseline characteristics recorded at screening visit will be presented in summary tables and listings for populations of interest.

8.1 Demographics and Subject Characteristics

The following continuous variables will be summarized using descriptive statistics by treatment group:

- Age (years)
- Height (cm)
- Weight (kg)
- Body Mass Index, BMI (kg/m^2)

Age will be automatically calculated in the eCRF system based on the date of the informed consent visit and the year of birth considering whether birth date has passed the informed consent date or not. BMI will be automatically calculated in the eCRF system as: Weight (kg) / $[Height (m)]^2$ using weight and height from 'Weight' and 'Subject Characteristics' pages of the eCRF.

The following categorical variables will be summarized in contingency tables:

- Sex (Male, Female)
- Fertility status (if female – Childbearing potential, Sterility, Menopause)

- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not reported, Unknown)
- Race (Caucasian, African, Asian, Other)
- Smoking status (Never smokers, Former smokers, Current smokers, Unknown)
- Flu vaccination history within a year (Yes, No)

Summary tables will be presented for ITT, ITTI, and PK populations. Also data will be listed for the ITT population.

8.2 Clinical Characteristics

The following continuous variables will be summarized using descriptive statistics by treatment group:

- Duration from onset of illness to study drug administration (hours): [Start date/time of study drug administration] – [Date/time of onset of illness]
- Influenza symptoms score at screening: Average scores of respiratory, constitutional, systemic and total symptoms
- Body temperature (℃) at screening

The following categorical variables will be summarized in contingency tables:

- Influenza subtype (Influenza A/H1, Influenza A/H3, Influenza A/H1 and H3, Unknown, NA)
- Influenza confirmed (by cell culture, qPCR, both, no)
- Rapid kit test results (positive, negative)

When influenza A virus load from qPCR has quantitative value or less than Lower Limit of Quantification (LLoQ), then influenza is confirmed. However, when influenza A virus load from cell culture has only quantitative value, then influenza is confirmed by cell culture.

Summary tables will be presented for ITT, ITTI, and PK populations. Also data will be listed for the ITT population.

8.3 Viral Serology

At screening, the following viral serology assessments will be performed: Hepatitis B Surface Antibody (HBsAb), Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus Antibody, Human Immunodeficiency Virus (HIV). The results of HBsAb, HBsAg, and Hepatitis C Virus Antibody will be classified as “Negative”, “Gray zone”, “Positive” or “Not done” with specification. Also, the results of HIV will be classified as “Negative”, “Positive” or “Not done” with specification. A listing and table will be produced for the safety population.

8.4 Medical History

Medical history is defined as a medical event or condition that will be recorded as part of the subject’s medical history if the onset of the event occurs before the ICF is signed.

Medical history will be summarized by treatment group with number and percentage and displayed by System Organ Class (SOC) and Preferred Term (PT). SOCs will be presented in alphabetical order and within each SOC, the PTs will also be presented in alphabetical order in the ITT, ITTI and PK populations. Subjects that have more than one prevalence per PT within each SOC will be counted only once. Medical history will also be listed for the ITT population.

Medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or later, and the version number will be shown as a footnote on the corresponding tables and a listing.

9. Treatments and Medications

9.1 Prior and Concomitant Medications

Use of all medications (drugs taken from 30 days prior to randomization until Day 110 or EOS visit) will be

recorded in the subject's eCRF.

A prior medication is defined as any medication with end date prior to the exposure to study drug.

A concomitant medication is defined as any medication that is ongoing, or has an end date that is on or after the date of study drug infusion. The start date of a concomitant medication can be before or after the date of first infusion. If the last taken time of medication and study drug infusion are available, then the time will be considered with date in determining the prior/concomitant medication.

If a subject takes specific medication several times within specific period of observation (i.e. prior or concomitant), then that medication is only counted once within the period where it is taken.

Prior and concomitant medications will be summarized by treatment group for safety population with number and percentage and displayed by Drug Class (Level 2) and PT. Drug Class will be presented in alphabetical order and within each Drug Class, the PTs will also be presented in alphabetical order. At each level of subject summarization, a subject is counted only once if a subject reported one or more medication at that level. When Anatomical Therapeutic Chemical (ATC) Level 2 for Drug Class is not available, Level 1 will be used instead.

Prior and concomitant medications will be identified in a listing for the ITT and safety population.

For the purpose of inclusion in prior or concomitant medication tables, incomplete medication start and end dates will be imputed as described in Appendix 14.3.1. A listing will display actually recorded (no imputed) dates in eCRF.

Prior and concomitant medications will be coded using the ATC classification of World Health Organization Drug Dictionary (WHODD) version September 2017 or later, and the version number will be shown as a footnote on the corresponding tables and listings.

9.2 Study Drug Exposure

Study drug exposure will be summarized by treatment group with number and percentage of the subjects who received full dose, partial dose, or are not administered study drug. The planned and administered dose (mg) of study drug will be also summarized using descriptive statistics.
A listing will be provided by treatment group showing the details of study drug exposure including actual administered dose for each subject. The actual administered dose will be calculated as Dose (45mg/kg or 90mg/kg for CT-P27 groups and 90mg/kg for Placebo group)*Weight at screening if a subject was administered planned dose. In case, the recorded weight is not correct, the actual administered dose will be calculated using weight recorded on the deviation list. This analysis will be performed on the safety population.

9.3 Use of Drugs for Symptom Relief

Drugs for symptom relief will be confirmed based on the recorded medications with "Yes" for the question, 'Is this drug used for symptom relief?' of the 'Prior and Concomitant Medications' page of eCRF.

Drugs for symptom relief will be summarized in a table in a similar manner to the table of concomitant medication described in section 9.1 for the ITT population.

Incomplete start date/time or end date/time of drugs for symptom relief will be imputed as described in Appendix 14.3.2.

10. Efficacy Analysis

10.1 Primary Efficacy Analysis

The primary efficacy endpoint analysis will assess the time from the administration of study drug to resolution of influenza symptoms and fever. The Flu-iiQ™ and body temperature recorded in diary including records as

a part of suspicious ADE assessment will be used for the analysis. The Flu-iiQ™ is a validated questionnaire with four domains. This includes the Domain 1; intensity of influenza symptoms, Domain 2; impact on activities, Domain 3; effects on feelings and Domain 4; concerns due to influenza. Subjects are offered four choices, ranging from the most positive response (e.g., none or not at all) to the most negative choice (e.g., severe or great difficulty). This analysis will be performed on the ITTI population.

The definitions of resolution of influenza symptoms and fever are described below.

Resolution of symptoms has occurred if all of the following influenza symptoms (as recorded on the Flu-iiQ^{TM} of Domain 1) are mild in intensity or none for at least 24 hours. (4-point scale - 0: None, 1: Mild, 2: Moderate, 3: Severe).

- Respiratory symptoms (cough, sore throat, and nasal congestion)
- Constitutional symptoms (headache, feeling feverish, body aches and pains, and fatigue)

Resolution of fever is defined as:

- Body temperature (as recorded in the diary) of <37.0℃ for at least 24 hours.

The start time for resolution of influenza symptom and fever is defined as the start time when symptoms and fever are resolved, whichever occurred latest.

The time (in days) from the administration of study drug to resolution of influenza symptoms and fever will be calculated as follows: [Start date/time of resolution of influenza symptoms and fever] – [Start date/time of study drug administration]. If time of completion of diary for Flu-iiQ^{TM} and body temperature is missing then the time will be assumed to be 10:00 AM and 10:00 PM for Morning and Evening, respectively.

If the subject has received the drugs for symptom relief, the effective duration of the drugs for symptom relief should be considered in determining the start time for resolution of symptom and fever.

For example, the study drug was administered at 12:00 on 1st day. The first time body temperature recorded <37.0℃ in the diary was 10:00 on 2nd day and continued more than 24 hours. But acetaminophen/ paracetamol known to be effective for 6 hours had been administered at 09:00 on 2nd day [1 hour prior to the time when the body temperature decreased <37.0℃], it will be calculated that the start time point for body temperature <37.0℃ is 15:00 on 2nd day [27 hours after the study drug administration]. Then, if the next time body temperature recorded <37.0℃ in the diary since 15:00 was 22:00 on 2nd day and body temperature was <37.0℃ for 24 hours from then, the start time for resolution of fever is 22:00 on 2nd day [34 hours after the study drug administration].

Drugs for symptom relief will be discussed during blinded DRM (14.5). Only drugs for symptom relief with an effective duration overlapping the primary endpoint duration (from a day of resolution start to resolution end) will be considered as drugs that affect the result of primary efficacy analysis. Effective durations of each drug will be discussed during blinded DRM too.

The primary efficacy endpoint will be analyzed using a Wilcoxon rank-sum test to assess differences between treatment groups (CT-P27 45 mg/kg vs placebo, CT-P27 90 mg/kg vs placebo), if every subject is followed until resolution of influenza symptoms and fever. The Wilcoxon rank-sum test will be used to test for a statistical significant difference of time to resolution between placebo and CT-P27. The results of the analysis will be summarized using p-values. The significant level will be set to 5%. If p-value is lower than 5%, it is considered that there is a significant difference between placebo and CT-P27. For subjects who withdrew from the study before the symptoms have resolved or if the symptoms did not resolve until the data cut-off, data will be censored at the latest date/time recorded on the diary or start date/time of study drug administration when there are no recorded data on the diary after study drug administration. If there is any censoring, the primary efficacy endpoint will be analyzed using Log-rank test and Gehans Wilcoxon test, and the result will be presented by p-values from the two tests. Also the table will present count of censoring reasons and 25th percentile, median, 75th percentile of time from administration of study drug to resolution. Kaplan-Meier plots will be presented.

If there are no censoring data, sensitivity analysis using tipping point analysis under Missing Not at Random (MNAR) will be also performed to explain varying cases about average unobserved outcomes dropouts on two treatment groups.

Sensitivity Analyses which alter resolution conditions of primary efficacy analysis will be performed on the ITTI population. Following two endpoints will be assessed as described for the primary efficacy endpoint.

- Time (in days) to resolution of influenza symptom (respiratory and constitutional symptoms)

In the analysis, fever is not considered and the definition of resolution of symptom is the same as those of primary efficacy analysis.

- Time (in days) to resolution of influenza symptom and fever

In the analysis, threshold of resolution of fever is changed to 37.8℃ and the definition o f resolution of symptom is the same as those of primary efficacy analysis.

10.2 Secondary Efficacy Analyses

The secondary efficacy endpoints will be analyzed on the ITTI and ITT populations. For time-to-event analyses of secondary efficacy endpoints, records on diary for suspicious ADE assessment and unscheduled assessment of site body temperature will be used together with data from regular scheduled assessment.

- The following secondary efficacy endpoints will be analyzed using a Kaplan Meier model to assess differences between placebo and CT-P27. Missing time of completion of diary will be considered as described in the section for the primary efficacy endpoint:
    - Time (in days) to resumption of normal activity as reported in Domain 2 of the Flu-iiQ^{TM}: [Start date/time of resumption of normal activity] – [Start date/time of study drug administration]

      The resumption of normal activity has occurred if the degree of difficulty of all of the Domain 2 items are of no difficulty or some difficulty for at least 24 hours.
    - Time (in days) to return to normal body temperature (<37.0℃) for at least 24 hours : [Start date/time of resolution of fever] – [Start date/time of study drug administration]

      Data of body temperature recorded on the diary as well as the ones measured from the sites will be used to determine the return time to normal body temperature for at least 24 hours.

      However, assessments which exceeds 24 hours measurement interval will be excluded because of lack of consecutiveness in determining the resolution.

      If time of measurement of body temperature from site is missing, then the time will be imputed based on time of study drug administration such that missing body temperature assessment time on Day 3 will be imputed as: Infusion time + 48 hours. Missing times on other days will be imputed in the same manner.
    - Time to resolution of individual symptoms for at least 24 hours as reported in Domain 1 of the Flu-iiQ^{TM}: [Start date/time of resolution of individual influenza symptoms] – [Start date/time of study drug administration]

      The resolution of individual influenza symptoms will be determined as described for the primary efficacy endpoint.
- Severity of symptoms as recorded on the Domain 1 of the Flu-iiQ^{TM}
    - Impact of influenza symptoms consist of 4 scales of the items in Domain 1 (respiratory symptoms, constitutional symptoms, systemic symptoms, total symptoms)
        - Respiratory symptoms: cough, sore throat, and nasal congestion

- Constitutional symptoms: headache, feeling feverish, body aches and pains, and fatigue
- Systemic symptoms: headache, feeling feverish, body aches and pains, fatigue, neck pain, interrupted sleep, and loss of appetite
- Total score: all items in Domain 1

Descriptive statistics of actual value and change from baseline for average score in each scale will be presented by treatment group at each visit.

If there are missing values in items in Domain 1, missing data will be handled according to section 10.3.

- Descriptive analysis for AUC of average symptom score from date of baseline assessment to last measurable value of subjects who have at least one post-baseline result.

  If there are missing values in average symptom scores between observed ones, the missing values are assumed to fall linearly between observed values.
- Mean daily symptom score on the Domain 1 of the Flu- iiQ^{TM}

  Average of total symptom score for each time point will be plotted with the SD of mean score.
- Incidence of symptoms on the Domain 1 with Grade 2 or Higher

  The proportion of subjects who developed any of the 7 individual influenza symptoms (cough, sore throat, nasal congestion, headache, feeling feverish, body aches and pains, and fatigue from Flu-iiQ^{TM} Domain 1) with moderately or severe in intensity (Grade 2 or higher) will be calculated from baseline to Day 8. Most severe score will be counted per each day. Subjects with incomplete data and no recorded symptoms will not be counted (i.e. did not experience symptoms Grade 2 or higher).

All item scores of Flu-iiQ^{TM} will be listed by each domain and time point. Additional listing for Flu-iiQ^{TM} will be provided including average score of Domain 1 (respiratory, constitutional, systemic, total symptom score), Domain 3, Domain 4 and AUC of Domain 1.

- Viral shedding in nasopharyngeal swab samples

  Viral shedding (titers) of swab samples based on qPCR and cell culture will be evaluated at the scheduled collection times. The listing will include titer results, whether the influenza A is confirmed and Area under the Curve (AUC) of viral loads. However, since cell culture results have information of both influenza A and B, the listing and tables for cell culture will present analysis results regardless of influenza type. Changes in viral shedding will be assessed as the change from baseline in $\log_{10}$vp/mL and $\log_{10}TCID_{50}$/mL for qPCR and cell culture respectively. If viral loads are lower than LLoQ (2.18 for qPCR), they will be treated as value without inequality sign. Whereas viral load lower than LLoQ for cell culture (0.75) will be considered as negative value and a negative value will be treated as 0. If the subtype of influenza A is “H1”, “NA” or “Unknown”, the virus titer from HA assay will be used for cell culture analysis. Otherwise, if the subtype is “H3”, the virus titer from NP ELISA will be used.

  These will be summarized for each treatment group and collection time.

  The following analyses will also be performed:

  - Summary of viral shedding results; percentage of subjects with positive/negative viral shedding at each visit (baseline, day 2, 3, 5, 8)
  - Duration (in days) of viral shedding; from date/time of baseline assessment to last positive sample. Subjects with at least one positive sample after baseline will be included in the summary.

- AUC of viral levels; from date of baseline assessment to last measurable value of subjects who have at least one post-baseline result (including BLQ (Below the Limit of Quantification) and negative values). If there are BLQ or missing values between measurable values, they are assumed to fall linearly between measurable values.
- Change from baseline in descriptive statistics of viral shedding of Swab Samples; descriptive statistics of actual value and change from baseline for viral shedding of swab samples will be presented by treatment group at each visit.
- Mean viral load titer (log values)
  Mean viral load titer for each scheduled time point will be plotted with the SD of mean value.

- Incidence of secondary complications of influenza

  The presence of secondary complications of influenza A infection will be determined by the Investigator's assessment of the subject's clinical condition. An Adverse Event (AE) will be considered as secondary complication if "Yes" is checked for the question, 'Is this Adverse event Secondary Complications of Influenza?' of the 'Adverse Event' page of eCRF.

  The number and percentage of subjects with secondary complications of influenza will be summarized by treatment group and PT. Secondary complications of Influenza will be summarized by SOC and PT, displaying the number and percentage of subjects with at least one secondary complications of Influenza. Secondary complications of influenza A will be listed including following variables: SOC, PT and reported term; Start date/time; End date/time; Duration of AE in days; Frequency; Outcome; Intensity; Relationship to study drug.

  The number and percentage of subjects with secondary complications of influenza who had used or never used antibiotics/antifungal/antiviral will be summarized by treatment group and overall for each PT of secondary complication AE. The summary of secondary complication AE will be presented in alphabetical order of PTs. The antibiotics/antifungal/antiviral for subjects with secondary complications will be discussed at the blind DRM. Algorithms for capture rule of the antibiotics/antifungal/antiviral is presented in Appendix 14.4.1 and ATC code list is presented in Appendix 14.4.2.

- QoL measures as reported in Domain 3 and Domain 4 of the Flu-iiQ™ (effect on feelings, concerns due to influenza)

  Each item will be scored with a 4-point scale (0: Not at all, 1: Somewhat, 2: Moderately, 3: Extremely), and the QoL will be presented as the average score of each domain, and will be summarized with descriptive statistics by collection time and treatment group.

- Physician Assessment

  Physician assessment including ears, nose, throat, sinuses, lungs, potential complications of Influenza will be performed at each scheduled time (Screening, Day 2, Day 3, Day 5, Day 8, Day 110/EOS). The results will be classified as "Normal", "Abnormal, NCS", "Abnormal, CS" or "Not done" with specification. The number and percentage of subjects regarding the result of physician assessment will be summarized by treatment group and system in the form of a shift table to detect changes from baseline in the ITT population. All physician assessment data will be listed for each subject by treatment group, visit, system and interpretation in the ITT population.

10.3 Missing Data Handling

10.3.1 Missing Data Handling for Primary Efficacy Analysis

When the Flu-iiQ™ has missing values (unanswered questions), two different approaches to handle the missing data will be taken to evaluate the impact of missing data on the primary efficacy results.

1) Missing data will not be imputed and only recorded Flu-iiQ™ will be used for the analysis.

2) On the other hand, missing data will be replaced by 0 or imputed using multiple imputation when at least one score on respiratory or constitutional symptoms in Domain 1 had been recorded.

Primary efficacy results from two different approaches will be compared to assess impact of missing imputation.

Prior to missing imputation, the number of missing values on a particular scale (respiratory or constitutional symptoms in Domain 1) will be considered in determining of way of imputation as follows:

2-1) If the number of missing items is less than half of the total number of items on a scale, missing values will be replaced by 0.

a. Respiratory symptom scale: if one of three items is missing, the other two recorded items will be used assuming a missing item has 0 value.

b. Constitutional symptom scale: if one of four items is missing, the other three recorded items will be used assuming a missing item has 0 value.

2-2) If the number of missing items is greater than or equal to half of the total number of items on a scale, multiple imputation will be conducted unless there is evidence that missing values would have 0 value.

2-2-1) Missing items are replaced by zero: when Flu-iiQ^{TM} is not complete, then reason of not done recorded in eCRF will be manually reviewed. If subjects had indicated that they had ceased to complete the questionnaire because their symptom had disappeared or completed the questionnaire only on days when they experienced symptoms, missing items since then will be replaced by zero.

2-2-2) Multiple imputation: for any other cases, missing data will be imputed using multiple imputation method assuming Missing at Random (MAR). Several imputed datasets created by multiple imputations will be pooled.

Missing body temperature from diary will not be imputed, but when 3 subsequent time points have only missing value for middle of the time points and subject data indicates resolution of fever at the other two time points, then it can be considered that fever has resolved. The following examples should be used for reference:

a. Example 1: Resolution of fever is considered to be maintained for 24 hours

Day 1 morning (10NOV16, 9:00 AM) Resolved
Day 1 evening (10NOV16, 9:00 PM) Missing
Day 2 morning (11NOV16, 9:00 AM) Resolved

b. Example 2: Resolution of fever is not considered to be maintained for 24 hours

Day 1 morning (10NOV16, 9:00 AM) Resolved
Day 1 evening (10NOV16, 9:00 PM) Missing
Day 2 morning (11NOV16, 9:00 AM) Missing
Day 2 evening (11NOV16, 9:00 PM) Resolved

10.3.2 Missing Data Handling for Secondary Efficacy Analyses

10.3.2.1 Time to Resumption of Normal Activity as Reported in Domain 2 of the Flu-iiQ™

If the number of missing items on Domain 2 is less than half of the total number of items on the domain, missing values will be replaced by 0 (same rule as 2-1 in section 10.3.1). Otherwise, it cannot be considered

that normal activity is resumed.

10.3.2.2 Time to Return to Normal Body Temperature (<37.0℃) for at Least 24 hours

Missing body temperature from diary or sites will not be imputed. However when there are missing values between two time-points with interval 24 hours at which normal body temperature are reported, it can be considered that fever is resolved for 24 hours.

10.3.2.3 Time to Resolution of Individual Symptoms for at Least 24 hours as Recorded on the Flu-iiQ™

The same rule for missing body temperature described in section 10.3.1 will be applied.

10.3.2.4 Severity of Symptoms as Recorded on the Flu-iiQ™

If the number of missing items on each scale of Domain 1 is less than half of the total number of items on the scale, only the recorded items are used for the analysis. Otherwise, data of that visit will be excluded from the analysis.

10.3.2.5 Quality of Life Measures as Reported in Domain 3 and Domain 4 of the Flu-iiQ™

The same rule as described in section 10.3.2.4 will be applied.

11. Exploratory Analysis

11.1 Pharmacokinetic Analysis

11.1.1 Serum Concentration

Blood samples will be collected from each subject during this study for the determination of the PK of CT-P27 components (CT-P22 and CT-P23) administered as 45 mg/kg and 90 mg/kg. Blood samples for PK analysis will be drawn according to the following schedule.

Day of study period	Time point	Window
Day 1	Pre-infusion	Within 15 minutes prior to the beginning of the infusion
	End of infusion	+15 minutes
	1 hour after EOI	± 15 minutes
Day 2	24 hours after SOI	
Day 3	48 hours after SOI	± 4 hours
Day 8	168 hours after SOI	
Day 15	336 hours after SOI	± 2 days
Day 29	672 hours after SOI	
Day 57	1344 hours after SOI	± 5 days
Day 110 or EOS visit	2616 hours after SOI or EOS visit	

Abbreviations: EOI, end of infusion; SOI, start of infusion; EOS, end of study

Serum samples will be analyzed to determine the concentrations of CT-P27 components (CT-P22 and CT-P23) using a validated immunoassay.

Serum concentrations of CT-P27 components (CT-P22 and CT-P23) will be summarized for PK population by treatment group at each scheduled collection time using descriptive statistics; n, mean, SD, geometric mean, CV%, minimum, median, and maximum values. Mean serum concentration-time profiles of study drug will be plotted by treatment on linear and semi-logarithmic scales based on scheduled sample times. Individual concentrations, scheduled timepoints/actual sample collection times and deviations from scheduled collection times will be presented in data listing by treatment in PK population. Individual linear and semi-logarithmic concentration-time plots (based on scheduled sample times) with respective treatments will also be presented together. Since the placebo group has BLQ values for serum concentration, it will not be

summarized in tables and figures.

The BLQ values prior to the study drug administration will be treated as zero (0). For the BLQ values after study drug administration, the following rules will be applied;

- The BLQ values at the beginning of a subject profile (i.e. before the first incidence of a measurable concentration) will be assigned to zero (0).
- The BLQ values at the end of a subject profile (i.e. after the last incidence of a measurable concentration) will be set to missing.
- Single or 2 consecutive BLQs which fall between two measurable concentrations will be set to missing.
- Two or more consecutive BLQs in terminal phase will be set to zero.

11.1.2 Serum Pharmacokinetic Parameters

PK parameters for CT-P27 components (CT-P22 and CT-P23) will be summarized at each dose level (45 mg/kg and 90 mg/kg) using descriptive statistics. Summary statistics will include the number of observations (n), mean, SD, geometric mean, CV%, minimum, median, and maximum. Since the placebo group has BLQ values for serum concentration, it will not be summarized in tables. Dose proportionality for CT-P22 and CT-P23 will be assessed. PK parameters will be computed by non-compartmental methods using the appropriate validated [redacted]. PK parameters will be summarized in the Follow-Up CSR only.

The following PK parameters will be calculated using non-compartmental methods for CT-P22 and CT-P23:

- $AUC_{0\text{-}last}$ (h・μg/mL) calculated using the linear trapezoidal rule. This will be calculated over the study period.
- C_{max} (μg/mL) obtained directly from the observed concentration versus time data.
- $AUC_{0\text{-}\infty}$ (h・μg/mL) calculated using the linear trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the terminal rate constant: $AUC_{0\text{-}last} + C_{last}/\lambda_z$.
- t_{max} (h) obtained directly from the observed concentration versus time data.
- C_{last} (μg/mL) obtained from the last observed quantifiable concentration.
- λ_z (1/h) determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile.
- t½ (h) determined as $\ln 2/\lambda_z$.
- MRT (h), determined as $AUMC_{0\text{-}\infty}/AUC_{0\text{-}\infty}$, where $AUMC_{0\text{-}\infty}$ is the area under the first-moment curve evaluated from time zero to infinite time.
- CL (L/h) calculated as the administered dose divided by $AUC_{0\text{-}\infty}$.
- V_z (L) calculated as Dose/($\lambda_z \cdot AUC_{0\text{-}\infty}$), where dose is the IV dose.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

$t_{1/2}$, Interval (h)	The time interval of the log-linear regression to determine $t_{1/2}$.
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z. A minimum of 3 data points will be used for determination.
Rsq	Coefficient of determination for calculation of λ_z. λ_z and related parameters ($AUC_{0\text{-}\infty}$, CL, MRT, $t_{1/2}$, V_z) will be listed and not summarized if Rsq is less than 0.800.
$\%AUC_{ex}$	Percentage of $AUC_{0\text{-}\infty}$ obtained by extrapolation, calculated as [(C_{last}/λ_z)/$AUC_{0\text{-}\infty}$×100]. If the extrapolated area (C_{last}/λ_z) is greater than 20% of

	$AUC_{0-\infty}$, then $AUC_{0-\infty}$ and related parameters (CL, MRT, V_z) will be listed and not summarized.
λ_z	If the interval used to determine λ_z is smaller than 1.5-fold the estimated $t_{1/2}$, λ_z and related parameters ($AUC_{0-\infty}$, CL, MRT, $t_{1/2}$, V_z) will be listed but not summarized.

Any anomalous concentration values observed at pre-dose will be identified in the study report and used for the computation of AUC. PK parameters will be computed if the anomalous value is not greater than 5% of the C_{max}. If the anomalous value is greater than 5% of C_{max}, only the concentration values will be listed and no PK parameters will be calculated or analyzed.

PK parameters will be presented in data listings and summarized in tables for PK population by treatment group. The decimal places for each PK parameter that will be presented in the listing are as follows:

PK parameter	The decimal places
$AUC_{0-\infty}$	1
AUC_{0-last}	1
C_{max}	1
C_{last}	1
t_{max}	2
V_z	2
λz	5
$t_{½}$	1
$t_{½}$, Interval	1
$t_{½}$, N	0
CL	4
MRT	2
Rsq	2
$\%AUC_{ex}$	1

Dose proportionality for CT-P22 and CT-P23 will be assessed for C_{max} and AUC_{0-last} using the Power model. For each of the parameters assessed, a plot of the log-transformed parameter value against the log-transformed dose will be constructed including the fitted line from the linear regression and the line of unity slope. The 95% confidence interval (CI) and P-value for the slope will be presented.

11.2 Immunogenicity Analysis

Immunogenicity will be assessed in the safety population by baseline and post-treatment serum measures of anti-CT-P27 component antibodies, CT-P22 and CT-P23 antibodies, using immunoassay. Immunogenicity assessments consist of both Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb) assays. The ADA

assay will follow a three-tiered approach consisting of (i) screening assay, (ii) specificity/confirmatory assay, and (iii) titration. The test outcome for the screening assay will be: {"Potential Positive" or "Negative"}. Samples that are "Potential Positive" in the screening assay will be undergone further testing in the specificity/confirmatory assay to determine if subjects are a true positive. The test outcome for the specificity/confirmatory assay will be: {"Reactive", "Negative", and "Not applicable (N/A)"}. "Reactive" indicates a true positive test outcome, "Negative" is considered negative and "N/A" indicates the assay was negative at the screening phase of the process. Subjects with a "Negative" test outcome for either screening or specificity/confirmatory assays will be considered negative for the overall ADA assessment. For further characterization, quantitative antibody level will be assessed by titration in confirmed positive samples. The ADA value of the CT-P22 and CT-P23 tagged assay will be transformed using a log transformation. Transformed ADA value can be obtained using $[\log_2(X/20)] + 1$ transformation.

Samples that are positive in the assessment will be analyzed further to conduct a NAb assessment. The same three-tiered approach of ADA assay will be applied to NAb assay. Transformed NAb value can be obtained using $[\log_2(X/10)] + 1$ transformation. If ADA or NAb titer values in the data are in inequality forms, the sign of inequality will be removed and then the values will be transformed.

Immunogenicity result for CT-P22 and CT-P23 are listed and summarized separately. The number and percentage of subject will be presented by treatment group and test at each scheduled time point for the safety population.

11.3 Other Exploratory Analysis

Blood sampling for assessment of anti-influenza antibodies (Hemagglutination inhibition) will be collected on Day 1 (at pre-infusion) and Day 29 (± 5days) or EOS visit (if a subject is early terminated from the study) in Subgroup (PK) Cohort.

Genotypic analysis on Hemagglutinin (HA) and Neuraminidase (NA) genes, and phenotype characterization of potential escape variants with regard to CT-P27 will be assessed using the nasopharyngeal swab samples.

11.3.1 HI Antibody

Individual HI antibody will be assessed repeatedly in each collection time (Baseline, Day 29) and the geometric mean value of those duplicated HI antibody results will be used in the analyses. The Geometric Mean Titer (GMT) and sample collection times will be presented in data listing by treatment group in PK population.

HI antibody will be summarized using geometric mean, minimum, median, and maximum of GMT values and Geometric Mean Fold Rise (GMFR; fold increase in GMT for Day 29 vs Baseline) by actual treatment group and each scheduled collection time. Also proportion of subjects with the titer values of Baseline <10 and Day 29≥40, Baseline>40, Day 29 >40, GMFR≥4, and Baseline≥10 and GMFR≥4 will be summarized.

The values below the LLoQ (10) will be imputed as 5 and the imputed values will be used for summary table.

11.3.2 Genotype

Genotype results will be presented in data listing by treatment group and subtype (H1N1 HA, H1N1 NA, H3N2 HA, H3N2, NA) in ITTI population.
Screening (influenza A positive sample regardless of titer value) and the last influenza A positive sample in time with > 4 $\log_{10}$vp/ml will be analysed.

11.3.3 Phenotype

Potential CT-P27 resistant variants will be selected by phenotypic virus titration assay. The result of this assay will be generated as a separate report.

Among potential variants, the samples for CT-P27 susceptibility and neuraminidase enzyme phenotyping assay will be selected in accordance with the central laboratory protocol. For potential variants, CT-P27 susceptibility assay and neuraminidase enzyme phenotyping assay will be performed to determine the half maximal effective concentration (EC_{50}) value for CT-P27 and the half maximal inhibitory concentration (IC_{50}) value for neuraminidase inhibitor (Oseltamivir), respectively. These values will be used to assess the resistance against CT-P27 and neuraminidase inhibitor. The fold resistance change which is the ratio of two resistance values will be presented with resistance values in data listing by treatment group in ITTI population. If one of values, EC_{50} or IC_{50}, has the Upper Limit of Quantification (ULoQ) the value will be treated as limit of quantification for the calculation of fold resistance change. All of results in the listing will be presented with 3 decimal places.

12. Safety Analysis

All safety analyses will be performed in the safety population by actual treatment group presenting data on AEs, Clinical laboratory results (Hematology, Biochemistry, Urinalysis), Vital signs, Immediate Hypersensitivity, ECG, Physical examination, Weight, Pregnancy test, Chest X-ray, Suspicious ADE.

12.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject enrolled (i.e., when the ICF is signed) into this study regardless to its causal relationship to study drug. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease.

All AEs will be classified by SOC and PT according to the MedDRA version 20.1 or later and the version number will be shown as a footnote on the corresponding tables and listings. AEs will be graded for intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 (Appendix 14.2).

Listings for AEs occurring during the study will be provided by actual treatment received. The listing will include the following information from the eCRF: SOC, PT and reported term; Start date/time; End date/time; Whether the event is classified as TEAE or TEAE due to Infusion Related/Anaphylactic Reaction (IRR) (Yes, No); Duration of AE in days (Duration= [End date-Start date] +1); Frequency (continuous, intermittent, transient, other with specified frequency); Outcome (recovered, recovered with sequelae, recovering, not recovered, fatal, unknown); Intensity (Grade 1(mild), Grade 2(moderate) Grade 3(severe), Grade 4(life-threatening), Grade 5(death)); Relationship to study drug (Definite, Possible, Probable, Unrelated, Not assessable); Action taken with study treatment (No action taken, Dose reduce, IP interrupted, IP withdrawn, Other with specified action); Other treatment (No treatment, Medication treatment, Non-medication treatment with specified treatment, Both medication and non-medication treatment with specified treatment); Whether a subject terminated from study due to this AE (Yes, No); Whether the event is serious (Yes, No); Whether the event is classified as secondary complication (Yes, No).
Events will be considered to be related if relationship is definite, possible, probable or not assessable for the study drug.

A summary table of overall AEs will be presented by actual treatment group, including the following:

- Total number of AEs, SAEs
- Number and percentage of subjects with at least one AE, SAE, TEAE, TESAE, TEAE leading to study discontinuation, TEAE due to IRR, TEAE leading to death.

A SAE is defined as any AE occurring at any dose that results in any of the following outcomes; death, life-threatening, in subject hospitalization or prolongation of existing hospitalization, disability/incapacity, congenital anomaly in the offspring of a subject who received drug, other SAEs; important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All SAEs will be listed including the variables detailed in the listing for AEs above except whether the event is serious (Yes, No).

Furthermore, additional information of SAEs will be listed in a separate listing including following variables: SOC, PT and reported term; Start date/time; End date/time; Whether the event is classified as TEAE or TEAE due to IRR; Serious criteria (hospitalization initial, hospitalization prolonged, life-threatening, results in death, persistent or significant/incapacity, congenital anomaly or birth defect, other medically important serious event); Admission date/Discharge date for hospitalized subjects; Death date; Autopsy performance (Yes, No); Death certificate completion (Yes, No) for subjects resulted death; SAE abating after stopping the study drug (Yes, No, NA); SAE description; SAE reoccurring after reintroduction of the study drug (Yes, No, NA).

12.1.1 Treatment-Emergent Adverse Event

A TEAE is defined as 1) a new event that occurs during or after treatment with study drug or 2) any event present at baseline that worsens in either intensity or frequency after exposure to study drug. If laboratory test abnormalities occur after the start of the administration of study drug, only clinically significant results will be considered to be TEAEs. Clinically significant cases are defined in section 6.2.1 of the protocol.
AEs that are checked “Post Dose” to the question ‘Is this AE occurred before first administration?’ in ‘Adverse Event’ page of the eCRF will be considered as TEAEs.

Total Number of TEAEs will be presented by actual treatment group. The number and percentage of subjects with at least one TEAE will be presented in total and by SOC, PT, relationship, intensity, and actual treatment group. The summary of TEAEs will be presented in alphabetical order of SOCs. Within each SOC, the PTs will also be presented in alphabetical order. At each level of summarization for the number of subjects with an event, a subject is counted only once if they reported one or more events and only the worst intensity will be counted. The following TEAE summaries will also be reported in separate tables.

- TEAEs considered to be related to study drug.
- TEAEs for at least 1% of subjects within PT among total treatment group.
- TEAEs with the intensity $\geq$Grade 3.

TEAEs considered to be related to study drug and TEAEs for at least 1% of subjects will be presented without relationship and intensity in summary tables.

12.1.1.1 Treatment-Emergent Adverse Events Leading to Study Discontinuation

TEAEs that are checked “Yes” to the question ‘Did the adverse event cause the subject to be discontinued from the study?’ in the ‘Adverse Event’ page of the eCRF will be considered as TEAEs leading to study discontinuation.

TEAEs leading to study discontinuation will be presented in a table in a similar manner to the tables of TEAEs described in section 12.1.1. Also, TEAEs leading to study discontinuation will be listed including the variables detailed in section 12.1 except whether a subject terminated from study due to this AE (Yes, No).

12.1.1.2 Treatment-Emergent Adverse Events due to Infusion Related/Anaphylactic Reaction

TEAEs that are checked “Yes” in ‘Is this Adverse event classified as an infusion related/anaphylactic reaction (IRR)?’ in the ‘Adverse Event’ page of the eCRF will be considered for this summary.
Table of TEAEs due to IRR will be presented in a similar manner to the tables of TEAEs described in section 12.1.1. TEAEs due to IRR will be listed including the variables detailed in section 12.1 with date/time of Blood Pressure (BP) assessment, Systolic Blood Pressure (SBP) (mmHg), Diastolic Blood Pressure (DBP) (mmHg) and comments except whether the event is classified as a secondary complication (Yes, No).

Also signs and symptoms of IRR will be presented in separate table and listing. The number and percentage of subjects with TEAE due to IRR and the number of events will be presented by actual treatment group and sign and symptom within category. A subject is counted only once if they reported one or more events. The

number of events at each level of summarization will be presented as well. Sign and symptom of IRR information will be listed including the following information from the eCRF: SOC, PT and reported term; Start date/time, End date/time, Category, Signs and Symptoms, and Intensity (Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), Grade 5 (death)). In case of 'Other' in eCRF, specified terms of signs and symptoms will be coded according to MedDRA, and SOC and PT will be listed as categories and signs and symptoms, respectively, instead of recorded ones in eCRF. Coded categories and symptoms in Appendix 14.6 will be confirmed during blind DRM.

12.1.2 Treatment-Emergent Serious Adverse Event

TESAEs will be presented in a table in a similar manner to the tables of TEAEs described in section 12.1.1.

12.2 Clinical Laboratory Analyses

Clinical laboratory (hematology, biochemistry, urinalysis) tests will be performed in local laboratories and results will be converted to standard units that are defined as in the sections 12.2.1, and 12.2.2.
Hematology, biochemistry and urinalysis parameters will be labeled with a CTCAE term and grading will be applied to post-baseline values for the parameters where possible according to CTCAE v 4.03. When CTCAE grade is upon clinical input only, the grading will not be applied, but grade require numeric and partial clinical input, grade will be assigned based on the numeric portion only. The CTCAE terms and grades for applicable parameters are listed in Appendix 14.2.1. The CTCAE grades for this analysis will be Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe) and Grade 4 (Life-threatening). The CTCAE Grade 5 (Death) will not be applied in this analysis since death cannot be determined from a numeric laboratory result. If the post-baseline result for a subject does not satisfy any CTCAE grade, it will be classified as "No Grade". If a laboratory parameter value falls within the local normal range, the grade will be classified as "No grade" even if the value has the numeric grade according to CTCAE v 4.03.

If the laboratory parameter value falls in outside the normal range: 'low' or 'high', they will be flagged in each visit. All hematology, biochemistry and numeric urinalysis data will be listed with high and low flags to show if a value is outside the normal range.

The results for all hematology, biochemistry and categorical urinalysis parameters will be categorized into Normal, Abnormal/Not Clinically Significant (NCS) or Abnormal/Clinically Significant (CS) using the local laboratory normal ranges used by study site and provided by local laboratory prior to analysis.
The number and percentage of subjects with a result for each grade will be summarized by CTCAE term, CTCAE grade and actual treatment group. The summary includes only the most severe case during the overall visits.

For the purpose of summarization, numeric laboratory parameters with inequality signs ('<' or '>') will be converted to numeric by removing the inequality sign and keeping only the numeric component of the result (e.g., result of '<2.6' would be converted to numeric '2.6'). The values which are converted to SI unit will be used in the analyses. If the maximum of decimal place for converted parameter is greater than or equal to 3, then the result is presented with 3 decimal places in the listing (but Eosinophil result is presented with 4 decimal places). The decimal places for descriptive statistics are presented based on the presented results in the listings.

12.2.1 Hematology

The following hematology laboratory tests will be included: White blood cells (WBC) (10^9/L), Red blood cells (RBC) (10^{12}/L), Hemoglobin (g/dL), Hematocrit (Proportion of 1.0), Platelet (10^9/L), Neutrophil (Proportion of 1.0), Lymphocyte (Proportion of 1.0), Monocyte (Proportion of 1.0), Eosinophil (Proportion of 1.0), Basophil (Proportion of 1.0), Absolute Neutrophil Count (ANC) (10^9/L). In addition, Absolute Lymphocyte Count (ALC) (10^9/L) will be calculated as follows: [WBC (10^9/L) * Lymphocytes (Proportion of 1.0)]. It will be presented in the listing with CTCAE grading and summarized in the CTCAE grading table, but will not be included in the hematology summary tables.

All hematology parameters will be summarized by parameter and actual treatment group for all scheduled collection times (Baseline, Day 3, Day 8) using descriptive statistics. Also, the additional shift table regarding the results of normality (Normal, Abnormal/NCS, and Abnormal/CS) will be summarized for all scheduled collection visit. All hematology test result data will be listed for each subject by actual treatment group, visit and individual test results.

12.2.2 Biochemistry

The following chemistry laboratory tests will be included: Albumin (g/L), Alkaline phosphatase (U/L), Alanine Aminotransferase (ALT) (U/L), Aspartate Aminotransferase (AST) (U/L), Blood Urea Nitrogen (BUN) (mmol/L), Chloride (mmol/L), Creatine Kinase (CK) (U/L), CK enzyme subtype (µg/L), Troponin (µg/L), Serum creatinine (µmol/L), Creatinine clearance (mL/min), C-reactive protein (nmol/L), Cholesterol (mmol/L), Glucose (mmol/L), Lactate Dehydrogenase (LDH) (IU/L), Potassium (mmol/L), Sodium (mmol/L), Total bilirubin (µmol/L), Direct bilirubin (µmol/L), Total protein (g/L), Uric acid (mmol/L), Triglyceride (mmol/L).

Biochemistry results will be presented in tables and listing in a similar manner to the tables and listing of hematology in section 12.2.1. Since relevant assessment for CK enzyme subtype and Troponin are performed only when CK result shows a clinical significance, they will not be summarized in visit based summary tables. Creatinine Clearance will be calculated using Cockcroft-Gault formula: [(140-Age)*Weight (in kilograms) * [0.85 if Female]] / [72*Serum Creatinine (in mg/dL)]. The Weight assessed at screening and calculated age using birth date and date of serum creatinine assessed at each visit will be used in the formula. Since the creatinine clearance was calculated using value of serum creatinine, additional normality for the creatinine clearance is not collected, therefore, the information will not be listed and summarized in a shift table.

12.2.3 Urinalysis

Numeric urinalysis parameters (pH, specific gravity) will be summarized by descriptive statistics for all scheduled collection times (Baseline, Day 3, Day 8). Categorical urinalysis parameters (Ketones, Protein, Glucose, Bilirubin, Nitrite, Urobilinogen, Occult Blood, Color) will be summarized in the form of shift table. Results of normality (Normal, Abnormal/NCS, and Abnormal/CS) will be summarized for all scheduled collection times.

Numeric and categorical parameters will be listed in separate listings. Both test result will be listed for each subject by actual treatment group, visit and individual test results.

If microscopic examination of sediment performed, the results will be listed.

12.3 Vital Signs

Vital signs of SBP, DBP, heart rate, respiratory rate, and body temperature will be summarized by actual treatment group, at each scheduled collection time (Baseline, Day 2, Day 3, Day 5, Day 8, and Day 110/EOS) using descriptive statistics. Changes from baseline will also be summarized by actual treatment group. Vital sign parameters with body temperature will be listed for each subject by actual treatment group, visit and individual test results.

12.4 Immediate Hypersensitivity

Vital sign parameters (SBP, DBP, respiratory rate, heart rate), body temperature and ECG measured for immediate hypersensitivity on Day 1 will be summarized by treatment group, at each scheduled collection time:

- Vital sign
  - Pre-infusion (within 15 minutes prior to the beginning of the infusion)
  - 30 minutes (±15 minutes) after the beginning of the infusion
  - Within 15 minutes after the end of the infusion
  - 1 hour (±15 minutes) after the end of the infusion

- 2 hours (±15 minutes) after the end of the infusion
- ECG
  - 1 hour (±15 minutes) after the end of the infusion

Immediate hypersensitivity findings will be classified as “Normal”, “Abnormal, NCS”, and “Abnormal, CS”. The results will be summarized by time point and actual treatment group with the number and percentage of subjects in each classification. The number and percentage of subjects who have a clinically notable vital sign and body temperature will be presented by actual treatment group, time point and parameter. The criteria for clinically notable results are defined as follows:

Parameter:

- SBP (mmHg): Low ≤90, High ≥160
- DBP (mmHg): Low ≤50, High ≥90
- Respiratory rate (breaths per minute): Low ≤12, High ≥20
- Heart rate (beats per minute): Low ≤50, High ≥100
- Body temperature (°C): Low ≤35.0, High ≥38.0

Data collected on monitoring for immediate hypersensitivity; vital sign, body temperature and ECG data will be listed by actual treatment group and time point.

12.5 Electrocardiogram

12-Lead ECG will be performed at screening, on Day 8, and Day 110/EOS. ECG findings will be classified as “Normal”, “Abnormal, NCS”, “Abnormal, CS”. The number and percentage of subjects will be summarized by actual treatment group and visit, in the form of a shift table to detect changes from baseline. All 12-Lead ECG data will be listed for each subject by actual treatment group and visit.

12.6 Physical Examination and Weight

Physical examination findings will be classified as “Normal”, “Abnormal, NCS”, “Abnormal, CS” or “Not done” with specification. The number and percentage of subjects will be provided by actual treatment group and body system, in the form of a shift table to detect changes from baseline. The following body systems will be examined;

- Head
- Neck
- Ear and Throat
- Thorax
- Abdomen
- Extremities
- Neurological System
- Skin and Mucosae

All Physical examination data will be listed for each subject by actual treatment group, visit and body system. Weight will be summarized in the form of change from baseline table by actual treatment group, at each scheduled collection time (Baseline, Day 110/EOS) using descriptive statistics. Weight will be listed with physical examination for each subject by actual treatment group and visit.

12.7 Pregnancy Test

Females of childbearing potential will have urine pregnancy test performed at screening by a local laboratory and will have an additional test for pregnancy at the end of the study (Day 110). If the urine pregnancy test gives equivocal results, a serum pregnancy test will be performed prior to study drug administration. Subjects

with a positive test result will be excluded from the study.

Urine pregnancy results will be classified as “Positive”, “Negative” or “Equivocal” and Serum pregnancy results will be “Positive” or “Negative”.

The pregnancy test by urine and serum pregnancy results will be summarized in a table by actual treatment group and visit showing the number and percentage of subjects. Percentages are calculated by using the number of female of child-bearing potential in the Safety population as the denominator. All pregnancy test result will be listed for each subject by actual treatment group, visit and individual test results.

12.8 Chest X-ray

Chest X-ray assessment will be performed at screening. If symptoms have not relieved up to Day 3, chest X-ray will be performed to determine presence of secondary complications of influenza A infection. Moreover, if the investigator considers chest X-ray is necessary, then it will be performed during the study to evaluate the lower respiratory tract. Findings will be classified as “Normal”, “Abnormal, NCS” or “Abnormal, CS”. The number and percentage of subjects regarding the result of chest X-ray assessment will be summarized by actual treatment group and visit in the form of a shift table to detect changes from baseline.

All chest X-ray result will be listed for each subject by actual treatment group and visit.

12.9 Suspicious ADE

Subjects will be considered to possibly have ADE if they meet any of the following criteria:

- Symptoms have not resolved or have worsened up to Day 8 after the administration of study drug in the opinion of the investigator
- The subject develops a secondary influenza-like illness after Day 8

Subjects with suspicious ADE will be required to assess virus titer using the nasopharyngeal swab sample, Flu-iiQ^{TM} and body temperature up to Day 8 after the day of ADE occurrence. If symptoms have not resolved or have worsened up to Day 8 after the day of ADE occurrence, same procedures will repeat.

The number and percentage of subjects who meet the criteria for suspicious ADE will be presented by actual treatment group.

Data recorded in ‘Suspicious ADE’ page of eCRF will be listed in listings for Flu-iiQ^{TM}, body temperature and virus titer of nasopharyngeal swab samples which are collected in scheduled visits.

13. Changes to Protocol-Specified Analysis

- The analysis scope for the 1st CSR is extended up to Day 110/EOS for subjects who enrolled in the first season to obtain sufficient data. (currently specified in 8.0 section of the protocol, but updated in 1.1 section of SAP)
- The definition of ITT population is changed to exclude subjects who are screening failures but randomized by accident. (currently specified in 8.4.1 section of the protocol, but updated in 5.3 section of the SAP)
- The definition of safety population is changed to include all subjects who receive any amount of study drug even if it’s only the normal saline solution but to analyze such subjects as the placebo group. (currently specified in 8.4.3 section of the protocol, but updated in 5.3 section of the SAP)
- The sensitivity analysis using tipping point analysis will be performed only when there is no censoring case. (currently specified in 8.6.1 section of the protocol, but updated in 10.1 section of the SAP)
- Handling of BLQ values after administration of study drug is updated. (currently specified in 8.5.3 section of the protocol, but updated in 11.1.1 section of the SAP)
- Description of %AUCex is updated according to the European Medicines Agency’s guidance in “GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE”. (CPMP/QWP/EWP/1401/98 Rev. 1)

(CHMP 2010). (currently specified in 8.5.3 section of the protocol, but updated in 11.1.2 section of the SAP)

- Senitivity analyses of primary efficacy analysis are added.

14. Appendices

14.1 Schedule of Assessments

Evaluation	Screening [1]	Treatment	Post-Treatment							
		Day 1	Day 2	Day 3	Day 5	Day 8	Day 15 (±2 days)	Day 29 (±5 days)	Day 57 (±5 days)	Day 110 / EOS visit[22] (±5 days)
Informed Consent	X									
Demographic, medical history, and height	X									
Inclusion/exclusion criteria	X									
Physical examination and weight	X									X
Hepatitis B/C and HIV tests (local)	X [2]									
Urine pregnancy test (local) [3]	X [4]									X
Clinical laboratory analyses [5] (local)	X [6]			X		X				
Vital Signs (blood pressure, heart rate, respiratory rate) [7]	X	X	X	X	X	X				X
12-Lead ECG [8]	X					X				X
Chest x-ray [9]	X			(X)[10]						
Randomization		X								
Infusion of CT-P27 or placebo [11]		X								
Blood sampling for PK (only Subgroup [PK] Cohort) [12]		X	X	X		X	X	X	X	X
Blood sampling for immunogenicity		X[13]								X
Blood sampling for HI antibody (only Subgroup [PK] Cohort)		X[13]						X		
Monitoring for immediate hypersensitivity [14]		X								
Collection of a nasopharyngeal swab [15]	X		X	X	X	X				
• Rapid influenza diagnostic test [16]	x									
• Virus titer (qPCR and Cell culture)	x		x	x	x	x				

Evaluation	Screening [1]	Treatment	Post-Treatment							
		Day 1	Day 2	Day 3	Day 5	Day 8	Day 15 (±2 days)	Day 29 (±5 days)	Day 57 (±5 days)	Day 110 / EOS visit[22] (±5 days)
• The characterization of isolated influenza viruses	x		(x)							
Physician assessment [17]	X		X	X	X	X				X
Flu-iiQ™ [18]	X	X								
Body Temperature [19]	X	X	X	X	X	X				X
Concomitant medication [20]	X	X (continuously throughout the study)								
Adverse events [21]	X	X (continuously throughout the study)								

ADE=antibody-dependent enhancement; AE=adverse event; ECG=electrocardiogram; eCRF=electronic case report form; EOS=End of Study; Flu-iiQ™=Influenza Intensity and Impact Questionnaire; HI=hemagglutination inhibition; HIV=Human immunodeficiency virus; PK=pharmacokinetic

Note: The assessments designated with an (X) will only be performed in selected subjects under the conditions explained in the footnotes.

1. For most subjects, obtainment of the informed consent form (ICF), screening for eligibility, randomization and treatment will occur on the same day. Though obtainment of the ICF may occur on the day prior to screening, randomization or treatment, it must be within 24 hours before the administration of study drug.
2. Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis C virus antibody, and HIV will be assessed at screening in all subjects (mandatory). The results of these tests are not intended as eligibility assessments, but collected to provide baseline information.
3. For females of child-bearing potential only.
4. Urine pregnancy test will be performed at screening. If the urine pregnancy test gives equivocal results, a serum pregnancy test will be performed prior to study drug administration. Subjects with a positive test result will be excluded from the study.
5. Clinical laboratory analysis will be performed at screening and on Day 3, Day 8. All clinical laboratory analysis will be performed at the local laboratory. The laboratory tests to be performed are presented in Table 3 of CT-P27 2.2 protocol v5.0.
6. Clinical laboratory results will not be used for assessment of eligibility, but to establish baseline values.
7. Vital sign will be performed at screening, Day 1 (prior to infusion), Day 2 (±4 hours), Day 3 (±4 hours), Day 5 (±4 hours), Day 8 (±4 hours) and Day 110 (±5 days) after the start of the study drug infusion. Blood pressure (sitting) and heart rate will be measured after the subject has rested (sitting quietly) for at least 5 minutes.
8. 12-Lead ECGs will be performed at screening, on Day 8 (±4 hours), and Day 110 (±5 days) (or EOS visit in early termination case).

9. Chest x-rays to evaluate the lower respiratory tract will be performed at screening and if the Investigator considers it is clinically appropriate, chest x-rays to evaluate the lower respiratory tract will be performed during the study.
10. If symptoms have not relieved up to Day 3, chest x-ray will be performed to determine presence of secondary complications of influenza A infection.
11. Treatment with study drug must occur no more than 48 hours after the onset of symptoms. If the adjustments of visit schedule is required, additional 12 hours can be allowed (Maximum onset of illness: 60 hours).
12. PK blood sampling at:
    - Day 1: pre-infusion (within 15 minutes prior to the beginning of study drug infusion), at the end of infusion (within 15 minutes after the end of study drug infusion), and 1 hour (±15 minutes) after the end of the study drug infusion.
    - Day 2: 24 hours (±4 hours) after the start of the study drug infusion.
    - Day 3: 48 hours (±4 hours) after the start of the study drug infusion.
    - Day 8: 168 hours (±4 hours) after the start of the study drug infusion.
    - Day 15 (±2 days), Day 29 (±5 days), Day 57 (±5 days), and Day 110 (±5 days)/EOS visit.
13. Day 1: prior to the study drug infusion.
14. On Day 1, vital signs (including blood pressure and heart rate, respiratory rate), body temperature and ECG will be assessed at the time points listed below, and the subject will be monitored continuously over the period for possible immediate hypersensitivity reactions.
    - Vital sign and body temperature
        - Pre-infusion (within 15 minutes prior to the beginning of the infusion).
        - 30 minutes (±15 minutes) after the beginning of the infusion.
        - Within 15 minutes after the end of the infusion.
        - 2 hour (±15 minutes) after the end of the infusion.
    - Vital sign, body temperature and ECG
        - 1 hour (vital sign, body temperature: ±15 minutes, ECG: −30/+60 minutes) after the end of the infusion.

    Emergency drugs and equipment suitable for assistance during anaphylactic reactions will be available during infusion with study drug.
15. When collecting the nasopharyngeal swabs, nasopharyngeal swabbing will be performed by trained site personnel. A nasopharyngeal swab sample will be obtained from all subjects up to Day 8 on the following schedule:
    - Screening (Nasopharyngeal swab samples will be collected for two times to be used for rapid influenza diagnostic test and virology assessment.)
    - Day 2: 24 hours (±4 hours) after the start of the study drug infusion.
    - Day 3: 48 hours (±4 hours) after the start of the study drug infusion.
    - Day 5: 96 hours (±4 hours) after the start of the study drug infusion.
    - Day 8: 168 hours (±4 hours) after the start of the study drug infusion.

16. Sponsor-supplied or agreed in advance rapid influenza diagnostic test material will be used. And if there is available test result confirmed as influenza A prior to obtaining written informed consent and that result was from the influenza diagnostic test which is agreed with Sponsor in advance, that test result can be allowed. At screening, testing must be performed within 24 hours before study drug administration. Subjects with a negative test result by rapid diagnostic test, who have onset of symptoms within 48 hours (window of +12 hours is allowed) before study drug administration, can be rescreened only once.
17. The Investigator or designee will perform a symptom-directed physical examination (which should include, at a minimum, the examination of ear, nose, throat, sinuses, and lungs) and assessment for potential complications of influenza.
18. The subject will record the results of the Flu-iiQ™ in the diary.
    - Flu-iiQ™ will be recorded once by the subject at the screening visit and will be recorded twice a day (at approximately 12-hour intervals) from Day 1 to Day 8 (in the morning [between 6 and 10 AM, approximately] and in the evening [between 6 and 10 PM, approximately]).
19. Body temperature which a subject experiences in prior to screening will be collected and body temperature taken with any type of thermometer will be acceptable. However, from the screening period, Sponsor-supplied thermometer will be used.
    - Temperature will be measured by subject; It will be recorded twice a day (at approximately 12-hour intervals) from Day 1 to Day 8 (in the morning [between 6 and 10 AM, approximately] and in the evening [between 6 and 10 PM, approximately]).
    - Temperature will be measured by site personnel at site: at screening, Day 1 (prior to infusion), Day 2 (±4 hours), Day 3 (±4 hours), Day 5 (±4 hours) and Day 8 (±4 hours).
    - These will be used for assessment of endpoint.
20. Use of all medications, from 30 days prior to randomization and up until Day 110/EOS visit, will be recorded in the subject's eCRF.
21. AEs will be collected from the date the informed consent form is signed until Day 110/EOS visit.
22. EOS visit will be done at Day 110. But if a subject is early terminated from the study, EOS visit will be done to assess safety parameters at any time.

Schedule of Assessments (Unscheduled Visits Subjects with Suspicious ADE)

Evaluation	Suspicious ADE Assessment				
	Day of occurrence[1]	Day 2	Day 3	Day 5	Day 8 [5]
Collection of a nasopharyngeal swab	X	X	X	X	X
• Virus titer (qPCR and Cell culture) [2]	x	x	x	x	x
• The characterization of isolated influenza viruses	x	(x)			
Flu-iiQ™[3]	X				
Body Temperature[4]	X				

1. The day of suspicious ADE occurrence.
   - Symptoms have not resolved or have worsened up to Day 8 (168 hours) after the administration of study drug in the opinion of the Investigator.
   - The subject develops a secondary influenza-like illness after Day 8 (168 hours).
2. Nasopharyngeal swab will be collected once a day up to Day 8 on the following schedule:
   - Day of occurrence
   - Day 2: 24 hours (±4 hours)
   - Day 3: 48 hours (±4 hours)
   - Day 5: 96 hours (±4 hours)
   - Day 8: 168 hours (±4 hours)
3. Flu-iiQ™ and the body temperature in the diary twice a day up to Day 8 (168 hours) from Day 1 to Day 8 (in the morning [between 6 and 10 AM, approximately] and in the evening [between 6 and 10 PM, approximately]).
4. Body temperature will be assessed by Sponsor-supplied thermometer.
5. If symptoms have not resolved or have worsened up to Day 8 after the day of ADE occurrence, same procedure will repeat.

14.2 CTCAE Grades

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

Note: Activities of Daily Living (ADL)

1. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
2. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.2.1 Laboratory Grades

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Hemoglobin	Low	<LLN - 10.0 g/dL	<10.0 - 8.0 g/dL	<8.0 g/dL	-
Alanine aminotransferase increased	Alanine Aminotransferase (ALT)	High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alkaline phosphatase increased	Alkaline phosphatase	High	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Aspartate aminotransferase increased	Aspartate Aminotransferase (AST)	High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Blood bilirubin increased	Total Bilirubin	High	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Cholesterol high	Cholesterol	High	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
CPK increased	Creatine Phosphokinase (CPK)	High	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Creatinine increased	Creatinine	High	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin increased	Hemoglobin	High	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-
Hyperglycemia	Glucose	High	Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L;	>27.8 mmol/L;
Hyperkalemia	Potassium	High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Hypernatremia	Sodium	High	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L;	>160 mmol/L
Hypertriglyceridemia	Triglyceride	High	1.71 mmol/L - 3.42 mmol/L	>3.42 mmol/L - 5.7 mmol/L	>5.7 mmol/L - 11.4 mmol/L	>11.4 mmol/L;
Hyperuricemia	Uric acid	High	>ULN - 10 mg/dL (0.59 mmol/L)	-	-	>0.59 mmol/L;
Hypoalbuminemia	Albumin	Low	<LLN - 30 g/L	<30 - 20 g/L	<20 g/L;	-
Hypoglycemia	Glucose	Low	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L
Hypokalemia	Potassium	Low	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Hyponatremia	Sodium	Low	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytosis	White blood cell (WBC)	High	-	-	>100,000/mm^3 ; (>100x$10e^9$ /L)	-
Lymphocyte count decreased	Lymphocyte	Low	<LLN - 800/mm^3; <LLN - 0.8 x $10e^9$ /L	<800 - 500/mm^3; <0.8 - 0.5 x $10e^9$ /L	<500 - 200/mm^3; <0.5 - 0.2 x $10e^9$ /L	<200/mm^3; <0.2 x $10e^9$ /L
Lymphocyte count increased	Lymphocyte	High	-	>4000/mm^3 - 20,000/mm^3; (>4 - 20x$10e^9$ /L)	>20,000/mm^3; (>20x$10e^9$ /L)	-
Neutrophil count decreased	Absolute Neutrophil Count (ANC)	Low	<LLN - 1.5 x $10e^9$ /L	<1.5 - 1.0 x $10e^9$ /L	<1.0 - 0.5 x $10e^9$ /L	<0.5 x $10e^9$ /L
Platelet count decreased	Platelet	Low	<LLN - 75.0 x $10e^9$ /L	<75.0 - 50.0 x $10e^9$ /L	<50.0 - 25.0 x $10e^9$ /L	<25.0 x $10e^9$ /L
Proteinuria	Protein	High	1+ proteinuria; urinary protein	Adults: 2+ proteinuria	-	-

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
White blood cell decreased	White blood cell (WBC)	Low	<LLN - 3.0 x $10e^9$ /L	<3.0 - 2.0 x $10e^9$ /L	<2.0 - 1.0 x $10e^9$ /L	<1.0 x $10e^9$ /L

Note: LLN= Lower Limit of Normal, ULN= Upper Limit of Normal

[1] Hyperglycemia was graded according to CTCAE which includes fasting glucose value although blood sample was taken regardless of fasting state.

[2] If suggested unit for CTCAE grading is not applicable to SI unit, it was converted to SI unit and applied.

[3] In case of numeric value for grading is identical such as Hypokalemia and Hyperuricemia, CTCAE grade which include numeric value only was applied, because abnormal laboratory value with clinical input was reported as an adverse event and graded accordingly.

14.3 Date Imputation

14.3.1 Prior and Concomitant Medication

Prior and concomitant medications will be coded using the WHO Drug Dictionary version Sep2017 or later. For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and end dates will be imputed as follows:

If the start date is incomplete, the following rules will be applied:

- If the day is missing (e.g. XXFEB2017), the month and year of the partial date will be compared to the date of illness onset.
    - If the month and the year are equal for both dates, the start date will be imputed as the earlier date of: (i) the date of illness onset, or (ii) the recorded end date of the medication. If the recorded end date is missing, the start date will be imputed as the date of illness onset.
    - If the month or year is not equal for both dates, the start date will be imputed as the first day of the month (e.g. 01FEB2017).
- If the day and month are missing (e.g. XXXXX2017), the year of the partial date will be compared to the date of illness onset.
    - If the years are equal for both dates, the start date will be imputed as the earlier date of: (i) the date of illness onset, or (ii) the recorded end date of the medication. If the recorded end date is missing, the start date will be imputed as the date of illness onset.
    - If the years are not equal for both dates, the start date will be imputed as the first day of January of the year (e.g. 01JAN2017).

If the end date is incomplete the following rules will be applied:

- If the day is missing (e.g. XXFEB2017), the month and year of the partial date will be compared to the date of End of Study (EOS).
    - If the month and the year are equal for both dates, the end date will be imputed as the later date of: (i) EOS, or (ii) the recorded/imputed start date of the medication.
    - If the month or year is not equal for both dates, the end date will be imputed as the last day of the month (e.g. 28FEB2017).
- If the day and month are missing (e.g. XXXXX2017), the year of the partial date will be compared to the date of End of Study (EOS).
    - If the years are equal for both dates, the end date will be imputed as the later date of: (i) EOS, or (ii) the recorded/imputed start date of the medication.
    - If the years are not equal for both dates, the end date will be imputed as the last day of the year (e.g. 31DEC2017).
- In the case of the death of a subject, if the imputed end date is after the date of death, the end date will be imputed as the date of death.

For the missing day imputation, the following examples should be used for reference:

- Example 1:

  Medication start: UNJUN2017
  Medication end: 20OCT2017
  Date of illness onset: 16OCT2017
  Medication start imputed: 01JUN2017

- Example 2:

Medication start: UNOCT2017
Medication end: 20OCT2017
Date of illness onset: 16OCT2017
Medication start imputed: 16OCT2017

- Example 3:

  Medication start: UNOCT2017
  Medication end: 20OCT2017
  Date of illness onset: 24OCT2017
  Medication start imputed: 20OCT2017

14.3.2 Symptom Relief Medication

The start date imputation will follow the same rules applied for the prior and concomitant start dates.
The end date imputation will also follow the same rules applied for the prior and concomitant end dates, except that the partial dates will be compared to the dates of Day 8 instead of EOS. For subjects with suspicious ADE, the same rules will be applied, but last date of suspicious ADE assessment will be used instead of Day 8.
To determine the start time for resolution of symptom and fever in primary efficacy analysis, incomplete first and last taken time of symptom relief drug will be imputed as follows:

Route	Frequency	Time of first taken	Time of last taken
Oral Respiratory(Inhalation) Intramuscular Ophthalmic	Once, Daily	08:00	08:00
	BID	08:00	20:00
	TID	08:00	20:00
Intravenous	Once, Daily	08:00	23:59
	BID	08:00	23:59
	TID	08:00	23:59

※ If a symptom relief drug was administered once intravenously and single dose is 2g then missing last taken time will be imputed as the first taken time.

14.4 Use of Antibiotics/Antifungal/Antiviral for Subjects with Secondary Complications

14.4.1 Algorithm for Capture Rule for Antibiotics/Antifungal/Antiviral

For summary of antibiotics (including antifungal and antiviral) use for subjects with secondary complication of influenza A infection, 4 steps are applied as follows:

Step 1. Capture the secondary complications.
Step 2. Capture medication use.

In the 'Adverse Event' page of the eCRF, "Medication treatment" or "Both medication and non-medication Treatment, specify" is selected for the question, 'Other Treatment'.

Step 3. Capture the medication related with secondary complications.

Medication start date recorded in the 'Prior and Concomitant Medications' page of the eCRF is between AE start and end date. (AE Start Date $\leq$ Medication Start Date $\leq$ AE End date)

Plus, indication of medication is the same as the term of AE.

Step 4. Capture the antibiotics/antifungal/antiviral.

The ATC codes listed in the Appendix 14.4.2 will be used to capture the antibiotics/antifungal/antiviral.

14.4.2 ATC Code List for Antibiotics/Antifungal/Antiviral

Following ATC Codes (WHODD version September 2017) list for antibiotics will be confirmed at the blind DRM.

Level 2	WHODD code (Level 4)
J01 Bacterials for systemic use	J01AA Tetracyclines
J01 Bacterials for systemic use	J01BA Amphenicols
J01 Bacterials for systemic use	J01CA Penicillins with extended spectrum
J01 Bacterials for systemic use	J01CE Beta-lactamase sensitive penicillins
J01 Bacterials for systemic use	J01CF Beta-lactamase resistant penicillins
J01 Bacterials for systemic use	J01CG Beta-lactamase inhibitors
J01 Bacterials for systemic use	J01CR Combinations of penicillins, inc. beta-lactamase inhibitors
J01 Bacterials for systemic use	J01DB First-generation cephalosporins
J01 Bacterials for systemic use	J01DC Second-generation cephalosporins
J01 Bacterials for systemic use	J01DD Third-generation cephalosporins
J01 Bacterials for systemic use	J01DE Fourth-generation cephalosporins
J01 Bacterials for systemic use	J01DF Monobactams
J01 Bacterials for systemic use	J01DH Carbapenems
J01 Bacterials for systemic use	J01DI Other cephalosporins and penems
J01 Bacterials for systemic use	J01EA Trimethoprim and derivatives
J01 Bacterials for systemic use	J01EB Short-acting sulfonamides
J01 Bacterials for systemic use	J01EC Intermediate-acting sulfonamides
J01 Bacterials for systemic use	J01ED Long-acting sulfonamides
J01 Bacterials for systemic use	J01EE Combinations of sulfonamides and trimethoprim, incl. derivatives

J01 Bacterials for systemic use	J01FA Macrolides
J01 Bacterials for systemic use	J01FF Lincosamides
J01 Bacterials for systemic use	J01FG Streptogramins
J01 Bacterials for systemic use	J01GA Streptomycins
J01 Bacterials for systemic use	J01GB Other aminoglycosides
J01 Bacterials for systemic use	J01MA Fluoroquinolones
J01 Bacterials for systemic use	J01MB Other quinolones
J01 Bacterials for systemic use	J01RA Combinations of antibacterials
J01 Bacterials for systemic use	J01WA Herbal antibacterials for systemic use
J01 Bacterials for systemic use	J01WB Herbal urinary antiseptics and antiinfectives
J01 Bacterials for systemic use	J01XA Glycopeptide antibacterials
J01 Bacterials for systemic use	J01XB Polymyxins
J01 Bacterials for systemic use	J01XC Steroid antibacterials
J01 Bacterials for systemic use	J01XD Imidazole derivatives
J01 Bacterials for systemic use	J01XE Nitrofuran derivatives
J01 Bacterials for systemic use	J01XX Other antibacterials
J02 Antimycotics for systemic use	J02AA Antibiotics
J02 Antimycotics for systemic use	J02AB Imidazole derivatives
J02 Antimycotics for systemic use	J02AC Triazole derivatives
J02 Antimycotics for systemic use	J02AW Herbal antimycotics for systemic use
J02 Antimycotics for systemic use	J02AX Other antimycotics for systemic use
J04 Antimycobactierals	J04AB Antibiotics
J05 Antivirals for systemic use	J05AA Thiosemicarbazones
J05 Antivirals for systemic use	J05AB Nucleosides and nucleotides excl. reverse transcriptase inhibitors
J05 Antivirals for systemic use	J05AC Cyclic amines
J05 Antivirals for systemic use	J05AD Phosphonic acid derivatives
J05 Antivirals for systemic use	J05AE Protease inhibitors
J05 Antivirals for systemic use	J05AF Nucleoside and nucleotide reverse transcriptase inhibitors
J05 Antivirals for systemic use	J05AG Non-nucleoside reverse transcriptase inhibitors
J05 Antivirals for systemic use	J05AH Neuraminidase inhibitors
J05 Antivirals for systemic use	J05AR Antivirals for treatment of HIV infections, combinations
J05 Antivirals for systemic use	J05AX Other antivirals
J05 Antivirals for systemic use	J05WA Herbal antivirals for systemic use
N04 Anti-parkinson drugs	N04BB Adamantane derivatives
R02 Throat preparations	R02AB Antibiotics

S02 Otologicals	S02AA Antiinfectives
S02 Otologicals	S02AW Herbal antiinfectives
S02 Otologicals	S02CA Corticosteroids and antiinfectives in combination
S03 Ophthalmological and otological preparations	S03AA Antiinfectives
S03 Ophthalmological and otological preparations	S03CA Corticosteroids and antiinfectives in combination

14.5 Drugs for Symptom Relief and Effective Duration

Drug (PT)	Effective Duration (Hours)
ACETYLCYSTEINE	12
ACTIFED /00005601/	12
BENZYDAMINE HYDROCHLORIDE	12
CEFDITOREN PIVOXIL	8
CEFRADINE	12
CHLORPHENAMINE	6
CHLORPHENAMINE MALEATE	6
CODENA-S	8
DESLORATADINE	24
DEXIBUPROFEN	12
DICLOFENAC	24
ELECTROLYTES NOS W/GLUCOSE	0
ERDOSTEINE	12
FLUOROMETHOLONE ACETATE	6
FLUTICASONE FUROATE	24
GLUCOSE	0
LEVOCETIRIZINE DIHYDROCHLORIDE	32
LEVODROPROPIZINE	6
LEVOFLOXACIN	8
MONTELUKAST	24
PARACETAMOL	6 (Single dose : 100 mg, 300 mg, 500 mg, 1000 mg)
	8 (Single dose : 650 mg, 1300 mg)
PETHIDINE	8
PHENIRAMINE	24
PREDNISOLONE	24
PROPACETAMOL HYDROCHLORIDE	12
PSEUDOEPHEDRINE	12

HYDROCHLORIDE	
SODIUM CHLORIDE	0
THEOBROMINE	12
TRAMADOL	6
TRAMADOL HYDROCHLORIDE	6
TROPHAMINE /02659801/	0
ZIPEPROL DIHYDROCHLORIDE	12

14.6 Coding of Categories and Signs and Symptoms for TEAEs due to IRR

The following table includes the mapping for re-coding of category "Other" based on MedDRA ver 20.1.

Previous Category	Previous Sign and Symptom	New Category	New Sign and Symptom
Other	Diarrhea	Gastrointestinal disorders	Diarrhoea
Other	Hiccup	Respiratory, thoracic and mediastinal disorders	Hiccups

14.7 List of Tables, Listings, Figures

List of Tables

Table Number	Population	Table Description	Source Listing
14.1.1	ITT	Summary of Analysis Populations	Listing 16.2.1.1 Analysis Population
14.1.2	ITT	Summary of Subject Disposition	Listing 16.2.1.2 Screening Failure, Listing 16.2.4.1 Subject Disposition, Listing 16.2.1.3 End of Study
14.1.3.1	ITT	Summary of Demographics and Subject Characteristics	Listing 16.2.4.2 Demographic and Subject Characteristics
14.1.3.2	ITTI	Summary of Demographics and Subject Characteristics	Listing 16.2.4.2 Demographic and Subject Characteristics
14.1.3.3	PK	Summary of Demographics and Subject Characteristics	Listing 16.2.4.2 Demographic and Subject Characteristics
14.1.4.1	ITT	Summary of Clinical Characteristics	Listing 16.2.4.3 Clinical Characteristics, Listing 16.2.6.1.1 Flu-iiQ: Average score and AUC
14.1.4.2	ITTI	Summary of Clinical Characteristics	Listing 16.2.4.3 Clinical Characteristics, Listing 16.2.6.1.1 Flu-iiQ: Average score and AUC
14.1.4.3	PK	Summary of Clinical Characteristics	Listing 16.2.4.3 Clinical Characteristics, Listing 16.2.6.1.1 Flu-iiQ: Average score and AUC
14.1.5	Safety	Summary of Hepatitis B/C and HIV Test	Listing 16.2.4.5 Hepatitis B/C and HIV Test
14.1.6.1	ITT	Summary of Medical History	Listing 16.2.4.6 Medical History
14.1.6.2	ITTI	Summary of Medical History	Listing 16.2.4.6 Medical History

14.1.6.3	PK	Summary of Medical History	Listing 16.2.4.6 Medical History
14.1.7	Safety	Summary of Prior Medications	Listing 16.2.4.8.2 Prior and Concomitant Medications
14.1.8	Safety	Summary of Concomitant Medications	Listing 16.2.4.8.2 Prior and Concomitant Medications
14.1.9	Safety	Summary of Study Drug Exposure	Listing 16.2.5.1 Study Drug Administration
14.1.10	ITT	Use of Drugs for Symptom Relief	Listing 16.2.4.8.1 Prior and Concomitant Medications
14.2.1.1	ITTI	Summary of Time to Resolution of Influenza Symptom and Fever - Wilcoxon Rank-Sum Test	Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.1 Flu-iiQ, Listing 16.2.6.2 Body Temperature from Diary
14.2.1.2	ITTI	Summary of Time to Resolution of Influenza Symptom and Fever - Wilcoxon Rank-Sum Test (Imputation)	Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.1 Flu-iiQ, Listing 16.2.6.2 Body Temperature from Diary
14.2.1.1	ITTI	Summary of Time to Resolution of Influenza Symptom and Fever	Listing 16.2.1.3 End of Study, Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.1 Flu-iiQ, Listing 16.2.6.2 Body Temperature from Diary
14.2.1.2	ITTI	Summary of Time to Resolution of Influenza Symptom and Fever (Imputation)	Listing 16.2.1.3 End of Study, Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.1 Flu-iiQ, Listing 16.2.6.2 Body Temperature from Diary
14.2.1.3	ITTI	Summary of Time to Resolution of Influenza Symptom and Fever - Sensitivity Analysis (Tipping Point Analysis)	Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.1 Flu-iiQ, Listing 16.2.6.2 Body Temperature from Diary
14.2.1.4	ITTI	Summary of Time to Resolution of Influenza Symptom - Sensitivity Analysis	Listing 16.2.1.3 End of Study, Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.1 Flu-iiQ

14.2.1.5	ITTI	Summary of Time to Resolution of Influenza Symptom and Fever (<37.8℃) - Sensitivity Analysis	Listing 16.2.1.3 End of Study, Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.1 Flu-iiQ, Listing 16.2.6.2 Body Temperature from Diary
14.2.2.1	ITT	Summary of Time to Resumption of Normal Activity - Kaplan-Meier Model	Listing 16.2.1.3 End of Study, Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.1 Flu-iiQ
14.2.2.2	ITTI	Summary of Time to Resumption of Normal Activity - Kaplan-Meier Model	Listing 16.2.1.3 End of Study, Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.1 Flu-iiQ
14.2.3.1	ITT	Summary of Time to Resolution of Fever - Kaplan-Meier Model	Listing 16.2.1.3 End of Study, Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.2 Body Temperature from Diary, Listing 16.2.9.1 Vital Signs and Body Temperature
14.2.3.2	ITTI	Summary of Time to Resolution of Fever - Kaplan-Meier Model	Listing 16.2.1.3 End of Study, Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.2 Body Temperature from Diary, Listing 16.2.9.1 Vital Signs and Body Temperature
14.2.4.1	ITT	Summary of Time to Resolution of Individual Influenza Symptom - Kaplan-Meier Model	Listing 16.2.1.3 End of Study, Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.1 Flu-iiQ
14.2.4.2	ITTI	Summary of Time to Resolution of Individual Influenza Symptom - Kaplan-Meier Model	Listing 16.2.1.3 End of Study, Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.1 Flu-iiQ
14.2.5.1	ITT	Change from Baseline in Descriptive Statistics of Influenza Symptoms (Flu-iiQ Domain 1) - Respiratory Symptoms	Listing 16.2.6.1.1 Flu-iiQ : Average Score and AUC

14.2.5.2	ITTI	Change from Baseline in Descriptive Statistics of Influenza Symptoms (Flu-iiQ Domain 1) - Respiratory Symptoms	Listing 16.2.6.1.1 Flu-iiQ: Average Score and AUC
14.2.6.1	ITT	Change from Baseline in Descriptive Statistics of Influenza Symptoms (Flu-iiQ Domain 1) - Constitutional Symptoms	Listing 16.2.6.1.1 Flu-iiQ: Average Score and AUC
14.2.6.2	ITTI	Change from Baseline in Descriptive Statistics of Influenza Symptoms (Flu-iiQ Domain 1) - Constitutional Symptoms	Listing 16.2.6.1.1 Flu-iiQ: Average Score and AUC
14.2.7.1	ITT	Change from Baseline in Descriptive Statistics of Influenza Symptoms (Flu-iiQ Domain 1) - Systemic Symptoms	Listing 16.2.6.1.1 Flu-iiQ: Average Score and AUC
14.2.7.2	ITTI	Change from Baseline in Descriptive Statistics of Influenza Symptoms (Flu-iiQ Domain 1) - Systemic Symptoms	Listing 16.2.6.1.1 Flu-iiQ: Average Score and AUC
14.2.8.1	ITT	Change from Baseline in Descriptive Statistics of Influenza Symptoms (Flu-iiQ Domain 1) - Total	Listing 16.2.6.1.1 Flu-iiQ: Average Score and AUC
14.2.8.2	ITTI	Change from Baseline in Descriptive Statistics of Influenza Symptoms (Flu-iiQ Domain 1) - Total	Listing 16.2.6.1.1 Flu-iiQ: Average Score and AUC
14.2.9.1	ITT	Descriptive Statistics for AUC of Symptom Score	Listing 16.2.6.1.1 Flu-iiQ : Average Score and AUC
14.2.9.2	ITTI	Descriptive Statistics for AUC of Symptom Score	Listing 16.2.6.1.1 Flu-iiQ : Average Score and AUC
14.2.10.1.1	ITT	Summary of Viral Shedding Results from qPCR	Listing 16.2.6.3.1 Virus Titer Results from qPCR
14.2.10.1.2	ITTI	Summary of Viral Shedding Results from qPCR	Listing 16.2.6.3.1 Virus Titer Results from qPCR
14.2.10.2.1	ITT	Summary of Viral Shedding Results from Cell Culture	Listing 16.2.6.3.2 Virus Titer Results from Cell Culture
14.2.10.2.2	ITTI	Summary of Viral Shedding Results from Cell Culture	Listing 16.2.6.3.2 Virus Titer Results from Cell Culture
14.2.11.1.1	ITT	Descriptive Statistics of Duration of Viral Sheddings from qPCR	Listing 16.2.6.3.1 Virus Titer Results from qPCR

14.2.11.1.2	ITTI	Descriptive Statistics of Duration of Viral Sheddings from qPCR	Listing 16.2.6.3.1 Virus Titer Results from qPCR
14.2.11.2.1	ITT	Descriptive Statistics of Duration of Viral Sheddings from Cell Culture	Listing 16.2.6.3.2 Virus Titer Results from Cell Culture
14.2.11.2.2	ITTI	Descriptive Statistics of Duration of Viral Sheddings from Cell Culture	Listing 16.2.6.3.2 Virus Titer Results from Cell Culture
14.2.12.1.1	ITT	Descriptive Statistics of AUC of Viral Loads from qPCR	Listing 16.2.6.3.1 Virus Titer Results from qPCR
14.2.12.1.2	ITTI	Descriptive Statistics of AUC of Viral Loads from qPCR	Listing 16.2.6.3.1 Virus Titer Results from qPCR
14.2.12.2.1	ITT	Descriptive Statistics of AUC of Viral Loads from Cell Culture	Listing 16.2.6.3.2 Virus Titer Results from Cell Culture
14.2.12.2.2	ITTI	Descriptive Statistics of AUC of Viral Loads from Cell Culture	Listing 16.2.6.3.2 Virus Titer Results from Cell Culture
14.2.13.1.1	ITT	Change from Baseline in Descriptive Statistics of Viral Sheddings of Swab Samples from qPCR	Listing 16.2.6.3.1 Virus Titer Results from qPCR
14.2.13.1.2	ITTI	Change from Baseline in Descriptive Statistics of Viral Sheddings of Swab Samples from qPCR	Listing 16.2.6.3.1 Virus Titer Results from qPCR
14.2.13.2.1	ITT	Change from Baseline in Descriptive Statistics of Viral Sheddings of Swab Samples from Cell Culture	Listing 16.2.6.3.2 Virus Titer Results from Cell Culture
14.2.13.2.2	ITTI	Change from Baseline in Descriptive Statistics of Viral Sheddings of Swab Samples from Cell Culture	Listing 16.2.6.3.2 Virus Titer Results from Cell Culture
14.2.14.1	ITT	Summary of Presence of Secondary Complications of Influenza A	Listing 16.2.6.4 Secondary Complications of Influenza A
14.2.14.2	ITTI	Summary of Presence of Secondary Complications of Influenza A	Listing 16.2.6.4 Secondary Complications of Influenza A
14.2.15.1	ITT	Use of Antibiotics for Subjects with Secondary Complications	Listing 16.2.4.8.1 Prior and Concomitant Medications, Listing 16.2.6.4 Secondary Complication of Influenza A

14.2.15.2	ITTI	Use of Antibiotics for Subjects with Secondary Complications	Listing 16.2.4.8.1 Prior and Concomitant Medications, Listing 16.2.6.4 Secondary Complication of Influenza A
14.2.16.1	ITT	Change from Baseline in Descriptive Statistics of Effect on Feelings (Flu-iiQ Domain 3) - Total	Listing 16.2.6.1.1 Flu-iiQ: Average Score and AUC
14.2.16.2	ITTI	Change from Baseline in Descriptive Statistics of Effect on Feelings (Flu-iiQ Domain 3) - Total	Listing 16.2.6.1.1 Flu-iiQ: Average Score and AUC
14.2.17.1	ITT	Change from Baseline in Descriptive Statistics of Concerns due to Influenza (Flu-iiQ Domain 4) - Total	Listing 16.2.6.1.1 Flu-iiQ: Average Score and AUC
14.2.17.2	ITTI	Change from Baseline in Descriptive Statistics of Concerns due to Influenza (Flu-iiQ Domain 4) - Total	Listing 16.2.6.1.1 Flu-iiQ: Average Score and AUC
14.2.18	ITT	Shift Table of Physician Assessment	Listing 16.2.6.5 Physician Assessment
14.2.19.1	PK	Descriptive Statistics of Serum Concentration (μg /mL) of CT-P22	Listing 16.2.6.6.1 Individual Serum Concentration (μg /mL) of CT-P22
14.2.19.2	PK	Descriptive Statistics of Serum Concentration (μg /mL) of CT-P23	Listing 16.2.6.6.2 Individual Serum Concentration (μg /mL) of CT-P23
14.2.20.1	PK	Descriptive Statistics of Pharmacokinetic Parameters of CT-P22	Listing 16.2.6.7.1 Individual Pharmacokinetic Parameters of CT-P22
14.2.20.2	PK	Descriptive Statistics of Pharmacokinetic Parameters of CT-P23	Listing 16.2.6.7.2 Individual Pharmacokinetic Parameters of CT-P23
14.2.21.1	PK	Statistical Analysis to Assess Dose Proportionality of CT-P22	Listing 16.2.6.7.1 Individual Pharmacokinetic Parameters of CT-P22
14.2.21.2	PK	Statistical Analysis to Assess Dose Proportionality of CT-P23	Listing 16.2.6.7.2 Individual Pharmacokinetic Parameters of CT-P23
14.2.22	Safety	Summary of Immunogenicity Results	Listing 16.2.6.8.1 Immunogenicity Testing of CT-P22, Listing 16.2.6.8.2 Immunogenicity Testing of CT-P23
14.2.23	PK	Summary of HI Response Results	Listing 16.2.4.3 Clinical Characteristics, Listing 16.2.6.9 Individual HI Antibody

14.3.1.1	Safety	Summary of Overall Adverse Events	Listing 16.2.7.1 Adverse Events
14.3.1.2	Safety	Summary of Treatment-Emergent Adverse Events	Listing 16.2.7.1 Adverse Events
14.3.1.3	Safety	Summary of Related Treatment-Emergent Adverse Events	Listing 16.2.7.1 Adverse Events
14.3.1.4	Safety	Summary of Treatment-Emergent Adverse Events for at least 1% of Subjects	Listing 16.2.7.1 Adverse Events
14.3.1.5	Safety	Summary of Treatment-Emergent Adverse Events with the Intensity ≥Grade 3	Listing 16.2.7.1 Adverse Events
14.3.1.6	Safety	Summary of Treatment-Emergent Adverse Events Leading to Study Discontinuation	Listing 14.3.2.3 TEAE Leading to Study Discontinuation
14.3.1.7	Safety	Summary of Treatment-Emergent Adverse Events due to Infusion Related/Anaphylactic Reactions	Listing 14.3.2.4 TEAE due to Infusion Related/Anaphylactic Reactions
14.3.1.8	Safety	Summary of Treatment-Emergent Adverse Events due to Infusion Related/Anaphylactic Reactions (Signs & Symptoms)	Listing 14.3.2.5 TEAE due to Infusion Related/Anaphylactic Reactions: Additional Information (Signs & Symptoms)
14.3.2.1	Safety	Summary of Treatment-Emergent Serious Adverse Events	Listing 14.3.2.1 Serious Adverse Events
14.3.4.1	Safety	Summary of CTCAE grading	Listing 16.2.8.1 Hematology, Listing 16.2.8.2 Biochemistry, Listing 16.2.8.4 Urinalysis - Categorical Parameters
14.3.4.2	Safety	Change from Baseline in Descriptive Statistics of Hematology	Listing 16.2.8.1 Hematology
14.3.4.3	Safety	Shift Table of Hematology Results	Listing 16.2.8.1 Hematology
14.3.4.4	Safety	Change from Baseline in Descriptive Statistics of Biochemistry	Listing 16.2.8.2 Biochemistry
14.3.4.5	Safety	Shift Table of Biochemistry Results	Listing 16.2.8.2 Biochemistry
14.3.4.6	Safety	Change from Baseline in Descriptive Statistics of Urinalysis	Listing 16.2.8.3 Urinalysis - Numeric Parameters
14.3.4.7	Safety	Shift Table of Urinalysis Results	Listing 16.2.8.4 Urinalysis - Categorical Parameters

14.3.5.1	Safety	Change from Baseline in Descriptive Statistics of Vital Signs and Body Temperature	Listing 16.2.9.1 Vital Signs and Body Temperature
14.3.5.2	Safety	Summary of Immediate Hypersensitivity Monitoring Interpretation	Listing 16.2.9.2 Immediate Hypersensitivity - Vital Signs and Body Temperature, Listing 16.2.9.3 Immediate Hypersensitivity - Electrocardiograms
14.3.5.3	Safety	Summary of Clinically Notable Vital Signs and Body Temperature Results during Hypersensitivity Monitoring	Listing 16.2.9.2 Immediate Hypersensitivity - Vital Signs and Body Temperature
14.3.5.4	Safety	Shift Table of Electrocardiogram Findings	Listing 16.2.9.4 12-Lead Electrocardiograms
14.3.5.5	Safety	Shift Table of Physical Examination Findings	Listing 16.2.9.5 Physical Examination and Weight
14.3.5.6	Safety	Change from Baseline in Descriptive Statistics of Weight	Listing 16.2.9.5 Physical Examination and Weight
14.3.5.7	Safety	Summary of Pregnancy Test Results	Listing 16.2.9.6 Pregnancy Test
14.3.5.8	Safety	Shift Table of Chest X-ray	Listing 16.2.9.7 Chest X-ray
14.3.6	Safety	Summary of Suspicious Antibody-Dependent Enhancement	Listing 16.2.6.1 Flu-iiQ, Listing 16.2.6.2 Body Temperature from Diary, Listing 16.2.6.3.1 Virus Titer Results from qPCR, Listing 16.2.6.3.2 Virus Titer Results from Cell Culture

List of Data Listings

Listing Number	Population	Listing Description
16.2.1.1	ITT	Analysis Population

16.2.1.2	All subjects	Screening Failure
16.2.1.3	ITT	End of Study
16.2.2.1	ITT	Major Protocol Deviation
16.2.4.1	ITT	Subject Disposition
16.2.4.2	ITT	Demographic and Subject Characteristics
16.2.4.3	ITT	Clinical Characteristics
16.2.4.4	ITT	Rapid Influenza Diagnostic Test of Nasopharyngeal Swab Samples
16.2.4.5	Safety	Hepatitis B/C and HIV Test
16.2.4.6	ITT	Medical History
16.2.4.7	ITT	Inclusion/Exclusion Criteria
16.2.4.8.1	ITT	Prior and Concomitant Medications
16.2.4.8.2	Safety	Prior and Concomitant Medications
16.2.5.1	Safety	Study Drug Administration
16.2.6.1	ITT	Flu-iiQ
16.2.6.1.1	ITT	Flu-iiQ: Average Score and AUC
16.2.6.2	ITT	Body Temperature from Diary
16.2.6.3.1	ITT	Virus Titer Results from qPCR
16.2.6.3.2	ITT	Virus Titer Results from Cell Culture
16.2.6.4	ITT	Secondary Complication of Influenza A
16.2.6.5	ITT	Physician Assessment
16.2.6.6.1	PK	Individual Serum Concentration (μg /mL) of CT-P22

16.2.6.6.2	PK	Individual Serum Concentration (µg /mL) of CT-P23
16.2.6.7.1	PK	Individual Pharmacokinetic Parameters of CT-P22
16.2.6.7.2	PK	Individual Pharmacokinetic Parameters of CT-P23
16.2.6.8.1	Safety	Immunogenicity Testing of CT-P22
16.2.6.8.2	Safety	Immunogenicity Testing of CT-P23
16.2.6.9	PK	Individual HI Antibody
16.2.6.10.1	ITTI	Genotype - H1N1 Hemagglutinin (HA)
16.2.6.10.2	ITTI	Genotype - H1N1 Neuraminidase (NA)
16.2.6.10.3	ITTI	Genotype - H3N2 Hemagglutinin (HA)
16.2.6.10.4	ITTI	Genotype - H3N2 Neuraminidase (NA)
16.2.6.11.1	ITTI	Phenotype - CT-P27 Susceptibility
16.2.6.11.2	ITTI	Phenotype - Oseltamivir
16.2.7.1	Safety	Adverse Events
14.3.2.1	Safety	Serious Adverse Events
14.3.2.2	Safety	Serious Adverse Events: Additional Information
14.3.2.3	Safety	TEAE Leading to Study Discontinuation
14.3.2.4	Safety	TEAE due to Infusion Related/Anaphylactic Reactions
14.3.2.5	Safety	TEAE due to Infusion Related/Anaphylactic Reactions: Additional Information (Signs & Symptoms)
16.2.8.1	Safety	Hematology
16.2.8.2	Safety	Biochemistry
16.2.8.3	Safety	Urinalysis - Numeric Parameters

16.2.8.4	Safety	Urinalysis - Categorical Parameters
16.2.8.5	Safety	Urinalysis - Microscopic Examination
16.2.9.1	Safety	Vital Signs and Body Temperature
16.2.9.2	Safety	Immediate Hypersensitivity - Vital Signs and Body Temperature
16.2.9.3	Safety	Immediate Hypersensitivity - Electrocardiograms
16.2.9.4	Safety	12-Lead Electrocardiograms
16.2.9.5	Safety	Physical Examination and Weight
16.2.9.6	Safety	Pregnancy Test
16.2.9.7	Safety	Chest X-ray
16.2.10.1	ITT	General Comments

List of Figures

Figure Number	Population	Figure Description	Source Listing
14.2.1	ITTI	Summary of Time to Resolution of Influenza Symptom and Fever (Kaplan-Meier Plot)	Listing 16.2.5.1 Study Drug Administration, Listing 16.2.6.1 Flu-iiQ, Listing 16.2.6.2 Body Temperature from Diary
14.2.8.1.1	ITT	Mean (+/-SD) Daily Total Symptoms Score	Listing 16.2.6.1.1 Flu-iiQ: Average Score and AUC
14.2.8.1.2	ITTI	Mean (+/-SD) Daily Total Symptoms Score	Listing 16.2.6.1.1 Flu-iiQ: Average Score and AUC
14.2.8.2.1	ITT	Incidence of Symptoms Grade 2 or Higher from Baseline to Day 8	Listing 16.2.6.1 Flu-iiQ
14.2.8.2.2	ITTI	Incidence of Symptoms Grade 2 or Higher from Baseline to Day 8	Listing 16.2.6.1 Flu-iiQ

14.2.13.1.1	ITT	Mean (+/-SD) Viral Load Titer (log values) from qPCR	Listing 16.2.6.3.1 Virus Titer Results from qPCR
14.2.13.1.2	ITTI	Mean (+/-SD) Viral Load Titer (log values) from qPCR	Listing 16.2.6.3.1 Virus Titer Results from qPCR
14.2.13.2.1	ITT	Mean (+/-SD) Viral Load Titre (log values) from Cell Culture	Listing 16.2.6.3.2 Virus Titer Results from Cell Culture
14.2.13.2.2	ITTI	Mean (+/-SD) Viral Load Titre (log values) from Cell Culture	Listing 16.2.6.3.2 Virus Titer Results from Cell Culture
14.2.18.1	PK	Mean (+/-SD) Serum Concentrations-Time Profiles of CT-P22	Listing 16.2.6.6.1 Individual Serum Concentration (µg/mL) of CT-P22
14.2.18.2	PK	Mean (+/-SD) Serum Concentrations-Time Profiles of CT-P23	Listing 16.2.6.6.2 Individual Serum Concentration (µg /mL) of CT-P23
14.2.19.1	PK	Individual Serum Concentration-Time Profiles of CT-P22	Listing 16.2.6.6.1 Individual Serum Concentration (µg /mL) of CT-P22
14.2.19.2	PK	Individual Serum Concentration-Time Profiles of CT-P23	Listing 16.2.6.6.2 Individual Serum Concentration (µg /mL) of CT-P23
14.2.20.1	PK	Plot of Log-Transformed C_{max} and $AUC_{0\text{-last}}$ (for CT-P22) versus Log-Transformed Dose	Listing 16.2.6.7.1 Individual Pharmacokinetic Parameters of CT-P22
14.2.21.1	PK	Plot of Log-Transformed C_{max} and $AUC_{0\text{-last}}$ (for CT-P23) versus Log-Transformed Dose	Listing 16.2.6.7.2 Individual Pharmacokinetic Parameters of CT-P23

15. Role & Responsibilities

Role	Name	Responsibilities
Biostatistician	[redacted]	Responsible for conducting statistical analysis and managing all the relevant tasks
QC Biostatistician	[redacted]	Responsible for reviewing the statistical analysis results conducted by the Project Biostatistician

16. Applied SOPs

SOP No.	SOP Version_Effective date	SOP Name
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

17. Applied SDs

SD No.	SD Version_Effective date	SD Name
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]