Clinical Study Protocol

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 Number:	**CT-P27 2.2**
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Product:	**CT-P27**
Study Phase:	**Phase IIb**
Sponsor:	[redacted]
Sponsor Contact:	[redacted]
SAE Reporting and Data Center:	[redacted]

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Sponsor Signature for Protocol Approval

PROTOCOL 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: CT-P27 2.2

Sung Young Lee
CELLTRION, Inc., 23, Academy-ro,
Yeonsu-gu, Incheon,
22014 South Korea

Signature	Date

SYNOPSIS

Name of Sponsor/Company:	CELLTRION, Inc.		
Name of Finished Product:	CT-P27		
Name of Active Ingredient:	Human monoclonal antibodies CT-P22 and CT-P23		
Title of Study:	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:	CT-P27 2.2		
Study Site(s):	[redacted]		
Study Duration:	Approximately 16 weeks	**Phase:**	IIb

Test Product, Dose and Mode of Administration:
CT-P27 45 mg/kg or 90 mg/kg dose by single IV infusion over 90 minutes (±15 minutes)

Reference Therapy, Dose and Mode of Administration:
Placebo by single IV infusion over 90 minutes (±15 minutes)

Objectives:

Primary Objective:

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

Secondary Objectives

- To evaluate the additional efficacy and safety of CT-P27, including potential effects on the incidence of antibody-dependent enhancement (ADE)

Exploratory Objectives:

- To assess the pharmacokinetics (PK) of CT-P27 components (CT-P22 and CT-P23)
- To assess immunogenicity
- To assess the characterization of isolated influenza viruses

Sample Size:
Approximately 183 subjects with acute uncomplicated influenza A infection will be randomly assigned to the 45 mg/kg CT-P27, 90 mg/kg CT-P27 or placebo groups (70 subjects per CT-P27 treatment groups and 43 subjects in placebo group).

Main Selection Criteria:
Male or female subjects with a diagnosis of influenza A by a rapid influenza diagnostic test and onset of illness no more than 48 hours prior to the planned administration of study drug will be considered for enrollment in the study if they meet all of inclusion criteria and none of the exclusion criteria.

Inclusion Criteria:

Each subject must meet all the following criteria to participate in this study:

1. Subject is a male or female and aged 19 to 64 years, inclusive.
2. Subject can voluntarily provide a written informed consent.
3. Onset of illness no more than 48 hours prior to the planned administration of study drug. If the adjustments of visit schedule is required, additional 12 hours can be allowed (Maximum onset of illness: 60 hours).

Note: time of onset of illness is defined as the earlier of either (a) the time when the body temperature was first measured as ≥38.0ºC (≥100.4ºF) 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).

4. As reported by the subject and recorded on the Flu-iiQ™ completed at screening, the subject has at least two of the following symptoms (moderate to severe in intensity):
   a) Respiratory symptom (cough, sore throat, or nasal congestion) or
   b) Constitutional symptom (headache, feeling feverish, body aches and pains, or fatigue).
5. Subject has a fever ≥38.0ºC or ≥100.4ºF at screening or a history of fever within the 24 hours prior to screening and has received treatment with an antipyretic(s) in the 6 hours prior to screening.
6. Subject is diagnosed with influenza A at screening, using the Sponsor-supplied or agreed in advance rapid influenza diagnostic test. 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.
7. For both male and female subjects, the subject and his/her partner (if of childbearing potential) agree to use a highly effective method of contraception during the study and for 5 months after the administration of study drug.
   a) Male and female subjects and their partner who have been surgically sterilized for less than 6 months prior to the date of informed consent must agree to use a highly effective method of contraception during the study and for 5 months after the administration of study drug.
   b) Menopausal females must have experienced their last menstrual period more than 12 months prior to the date of informed consent to be classified as not of childbearing potential.
8. Subject's body mass index (BMI) is of <35.0 kg/m^2 and weight is of ≤99.9 kg.

Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from the study:

1. Subject is not likely to complete all required study visits or procedures for any reason, in the opinion of the Investigator.
2. Subject has received a treatment with another investigational medical product or participated in another clinical trial within 30 days (or 5 half-lives, whichever is longer).
3. Subject has previous exposure to any anti-influenza monoclonal antibody therapy including CT-P27 prior to study drug administration.
4. Subject has a history of hypersensitivity to any monoclonal antibody or has a known hypersensitivity to any of the treatment components.
5. Subject is taking antiviral treatment for influenza (e.g., zanamivir, oseltamivir, rimantadine, amantadine, peramivir, or ribavirin) or has a history of using these antivirals within 14 days prior to the administration of study drug.
6. Subject has been immunized against influenza with live attenuated or inactivated virus vaccine within 21 days prior to the administration of study drug.
7. Subject has a medical condition including one or more of the following:
   a. Positive influenza B or influenza A+B infection.
   b. History or presence of congestive heart failure with symptoms consistent with New York Heart Association Class III or IV functional status within 12 months prior to study drug administration.
   c. Presence of clinically significant abnormality on a 12-lead electrocardiogram (ECG) at screening that, in the Investigator's clinical judgment, may compromise the safety of the subject or affect

the outcome of the study. These include, but are not limited to, a PR interval >200 msec, a corrected QT interval [QTc] >450 msec for male subjects and >470 msec for female subjects, or any evidence of heart block, right bundle branch block, or left bundle branch block.

d. History or presence of any clinical condition or evidence of organ dysfunction that may affect either the subject's ability to participate in the study or the study result, in the opinion of the Investigator.

e. Subjects with abnormal liver function values. These will include aspartate transaminase (AST), alanine transaminase (ALT) or alkaline phosphatase (ALP) $\geq 3 \times$ ULN at screening.

f. Subject with abnormal renal function values (serum creatinine $\geq 1.7 \times$ ULN with creatinine clearance level $\leq$ 75mL/min at screening).

g. In the opinion of the Investigator, the subject has active tuberculosis.

h. Uncontrolled diabetes mellitus (defined as known by the case of HbA1c >8%).

i. Uncontrolled hypertension (defined as known by the case of systolic blood pressure (SBP) $\geq$160 mmHg or diastolic blood pressure (DBP) $\geq$100 mmHg).

j. Documented, known current infection with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).

k. Severe infection within 30 days prior to the administration of study drug that required parenteral antibiotic use or hospitalization.

l. Any uncontrolled acute or chronic clinically significant respiratory disease (e.g., chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, asthma, or bacterial pneumonia).

m. History of malignancy within 2 years prior to study drug administration (with the exception of treated basal cell carcinoma of the skin or carcinoma in situ of the cervix) or current active malignancy.

8. Subject is currently hospitalized or currently requires hospitalization due to severity of illness or has any plan for elective hospitalization within 1 month after study drug administration.
9. Subject requires oxygen therapy due to underlying disease or influenza infection.
10. Subject has a history of bone marrow or solid organ transplantation.
11. Subject uses systemic steroids or other immunosuppressant (except oral steroid up to 5-10 mg/day, methotrexate up to 10 mg/week).
12. Subject requires routine/intermittent hemodialysis or peritoneal dialysis.
13. Subject is pregnant or breastfeeding.
14. Subject is not eligible for the study participation for whatever reason (including clinical laboratory results) in the opinion of the Investigator, or shows evidence of a condition (psychological, emotional problems, any disorders or resultant therapy) that is likely to invalidate informed consent, or limited the ability of the subject to comply with the protocol requirements in the opinion of the Investigator, or unable to understand the protocol requirements, instructions and study related restrictions, the nature, scope and possible consequences of the clinical study, or is unable to give written informed consent or to comply fully with the protocol.

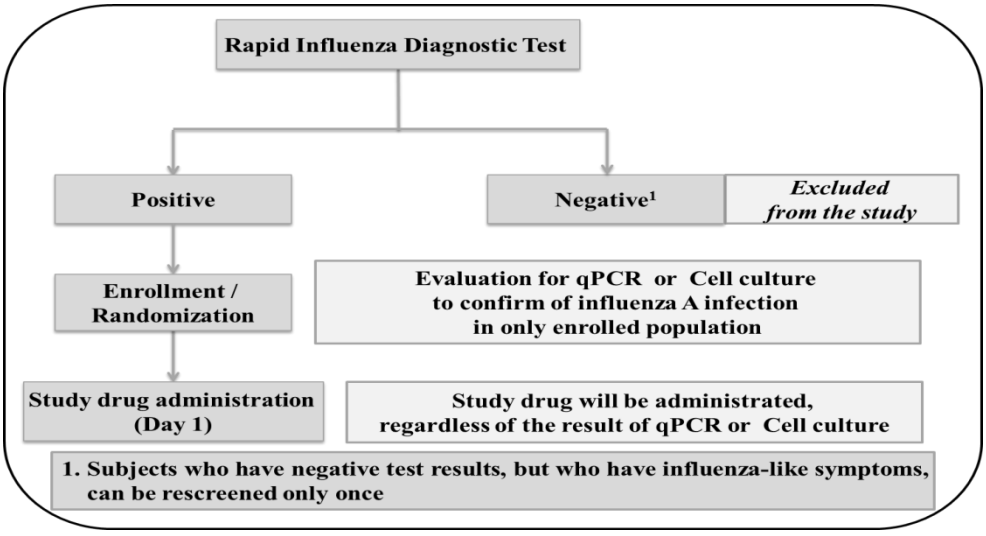
Methodology:

This is a Phase IIb, multicenter, placebo-controlled, randomized, double-blind, parallel-arm study to evaluate the efficacy and safety of 2 different 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). 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.

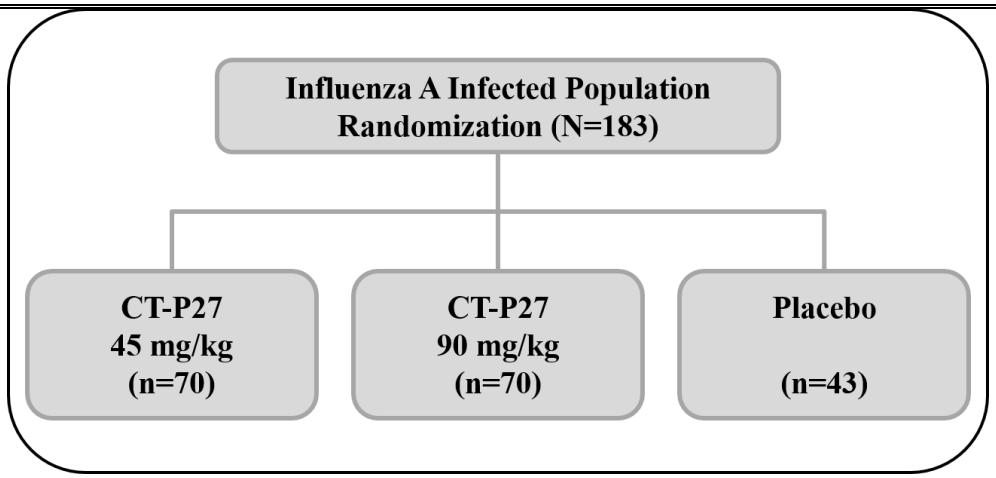
To be eligible for enrollment, subjects must have a positive test result for influenza A by a rapid influenza diagnostic test. At screening, nasopharyngeal swab samples will be collected for two times to be used for rapid influenza diagnostic test and virology assessment. The enrollment process is presented in **Figure S1.**

Figure S1 Enrollment Process



Approximately 183 subjects with influenza A to be enrolled in the study will be randomly assigned to 1 of 3 groups, 45 mg/kg CT-P27, 90 mg/kg CT-P27, or placebo (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 PK sub-study (Yes vs No). A schematic diagram of subject assignment is presented in **Figure S2.**

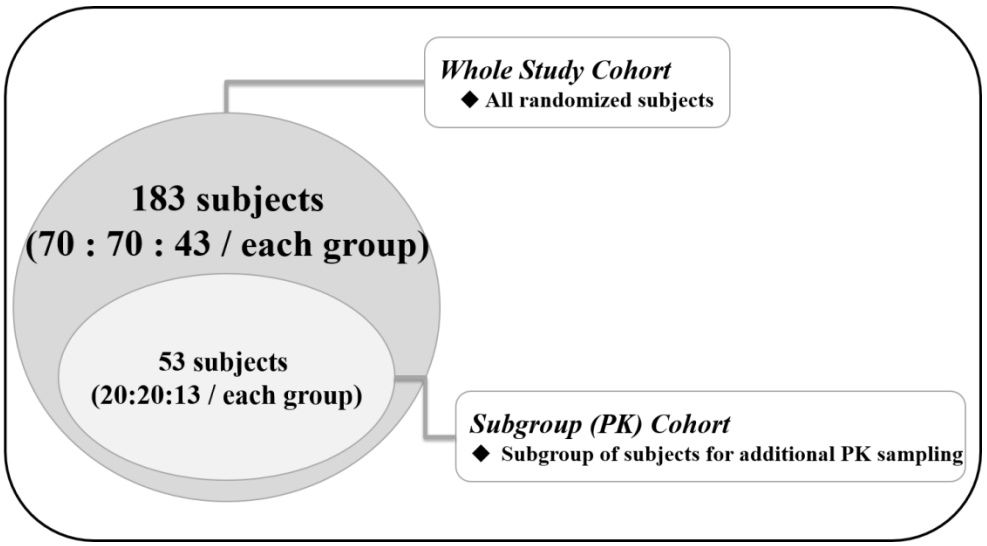
Figure S2 Schematic diagram of Subject Assignment



All enrolled subjects will be given a single dose of 45 mg/kg CT-P27, 90 mg/kg CT-P27, 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 S3.**

Figure S3 Schematic Diagram for the Study Cohorts



Subjects may be admitted in a hospital from Day 1 (before study drug administration) to Day 3 (after completion of the 48 hours assessments) if it is deemed necessary upon the judgement of the investigator.
Study visits:

- Subjects who are included in Whole Study Cohort and are hospitalized: 4 planned study visits
- Subjects who are included in Whole Study Cohort but are not hospitalized: 6 planned study visits
- Subjects who are included in the Subgroup (PK) Cohort and are hospitalized: 7 planned study visits
- Subjects who are included in the Subgroup (PK) Cohort but are not hospitalized: 9 planned study visits

Efficacy Assessment:

The completion of the Influenza Intensity and Impact Questionnaire (Flu-iiQ™) and the recording of body temperature will take place at screening for baseline assessments. After study drug administration, subjects will be instructed to complete the Flu-iiQ™ and the body temperature in the diary 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]) and body temperature of subject will be also taken by site personnel at site at screening, Day 1 (prior to infusion), Day 2, Day 3, Day 5 and Day 8.

Nasopharyngeal swab samples will be used for viral shedding based on quantitative polymerase chain reaction (qPCR) and cell culture. Those samples will be taken at screening, 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), and Day 8 (168 hours [±4 hours] after the start of the study drug infusion). Laboratory confirmation of influenza A infection will be defined as a positive result by qPCR or cell culture.

The following efficacy parameters will be assessed as primary and secondary 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.

Resolution of symptoms has occurred if the following influenza symptoms (as recorded on the Flu-iiQ™) 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°C 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°C) for at least 24 hours.
- Time to resolution of individual symptoms for at least 24 hours as recorded on the Flu-iiQ™.
- Severity of symptoms as recorded on 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™.

Safety Assessment:

For safety evaluations, subjects will be followed up from the time the ICF is signed until Day 110 (approximately 5 half-lives) after the administration of study drug. Safety assessments will occur throughout the study.

Adverse events (AE) or concomitant medications that are verified by the investigator will be recorded on the eCRF. Up to Day 8, any AE or concomitant medication will also be recorded by subjects on their diaries and the investigators will refer to the records for information. If there is any AE or concomitant medication after Day 8, subjects will be instructed to contact the principal investigator or sub-investigator at any time.

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.

Subjects with suspicious ADE will be required to assess virus titer using the nasopharyngeal swab sample, Flu-iiQ™ 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 following safety parameters are determined as secondary safety endpoints:

- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious adverse events (TESAEs)
- TEAEs leading to treatment discontinuation
- Clinical laboratory analyses (hematology, biochemistry, and urinalysis laboratory tests)
- Vital sign measurements
- ECGs
- Physical examination findings
- ADEs

Exploratory Assessment:
Blood sampling for PK analysis will be collected from the subjects on:

- Day 1 at pre-infusion (within 15 minutes prior to the beginning of the infusion), the end of infusion (+15 minutes), 1 hour (±15 minutes) after the end of the 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),
- Days 29, 57 and 110 (±5 days) or at End-of-Study (EOS) visit

Blood sampling for Immunogenicity assessment will be collected on Day 1(at pre-infusion) and Day 110 (± 5days) or EOS visit.

For the subjects with Influenza A confirmed by qPCR or cell culture, 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.

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.

Additional genotyping tests could be conducted if it is required from a regulatory or medical perspective.

The following parameters are determined as 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

- Anti-drug specific antibodies for CT-P27 component antibodies (CT-P22 and CT-P23)
- HI antibody
- Genotype and phenotype of isolated influenza virus

Sample Size Assumptions:

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 standard deviation (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.

Data Analysis:

Statistical Analysis:

Statistical analyses will be carried out [redacted]. Clinical parameters measured in this study will be described using descriptive statistics (including number [n], mean, median, SD, minimum, and maximum) for quantitative variables and frequency counts and percentages for qualitative variables. Data will be listed in data listings.

The detailed method about the statistical analysis will be described in a statistical analysis plan (SAP), which will be finalized prior to database lock and unblinding of the treatment codes. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the final clinical study report.

Analysis Populations:

- Intent-to-Treat (ITT) Population: defined as all subjects randomized to study drug or placebo.
- Intent-to-Treat Infected (ITTI) Population: defined as all randomized subjects with confirmed influenza A by qPCR or cell culture.
- Safety Population: defined as all randomized subjects receiving any amount of CT-P27 or placebo.
- Pharmacokinetic Population: defined as approximately 53 subjects (20 per CT-P27 treatment groups and 13 in placebo group) in Subgroup (PK) Cohort and 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.

Efficacy Analyses:

The primary efficacy endpoint will be analyzed on the ITTI population using a Wilcoxon's rank-sum test to assess differences between treatments, if every subject were followed until resolution of influenza symptoms and fever. The statistically significant difference of time to resolution of influenza symptoms and fever between placebo and CT-P27 based on Wilcoxon rank-sum test will be presented by p-values. If there is any censoring, the primary efficacy endpoint will be analyzed using Log-rank test, and Kaplan-Meier plots will be presented.

The secondary efficacy endpoints will be analyzed on both ITTI and ITT populations. Time to resumption of normal activity, return to normal body temperature (<37.0ºC) and resolution of individual symptoms will be analyzed using a Kaplan Meier model. Severity of symptoms, Incidence of secondary complications of influenza, viral shedding and QoL by Flu-iiQ™ will be summarized by treatment groups.

Safety Analyses:

Adverse events will be coded to system organ class and preferred term according to the Medical Dictionary for Regulatory Activities. Adverse events will be graded for severity based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Adverse events will be summarized using frequency tables presented by treatment group. The results of other safety analyses will be presented using descriptive statistics or shift tables, as appropriate. All safety analyses will be based on the safety population.

Exploratory Analyses:

Pharmacokinetic parameters will be computed by non-compartmental methods using [redacted]. Pharmacokinetic 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 and will include AUC_{0-last}, $AUC_{0-\infty}$, C_{max}, C_{last}, t_{max}, $t_{1/2}$, λ_z, MRT, CL, and V_z. Summary statistics will include the number of observations (n), mean, SD, median, minimum, maximum, geometric mean, and coefficient of variation (CV%). All PK analyses will be based on the PK population. Dose proportionality for CT-P22 and CT-P23 will be assessed for C_{max} and AUC_{0-last} 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) or P-value for the slope will be presented.

Anti-drug specific antibodies for CT-P27 component antibodies, genotype, phenotype, and HI antibody will be summarized by treatment group and time point. Analysis of anti-drug specific antibodies for CT-P27 component antibodies will be performed using safety population, and analysis of HI antibody will be performed using PK population. Analysis of genotype and phenotype will be performed using ITTI population.

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibodies
ADE	Antibody-dependent enhancement
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time zero to the last quantifiable concentration
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve in serum from time zero extrapolated to infinite time
$AUMC_{0\text{-}\infty}$	Area under the first moment-time curve in serum from time zero extrapolated to infinite time
BLQ	Below the limit of quantitation
BUN	Blood urea nitrogen
CK	Creatine kinase
CL	Systemic clearance from serum after intravenous dosing
C_{last}	Last observed quantifiable concentration
C_{max}	Maximum observed serum concentration
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of Variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EOS	End of Study
EU	European Union
FDA	Food and Drug Administration

Flu-iiQ™	Influenza Intensity and Impact Questionnaire
GCP	Good Clinical Practice
HA	Hemagglutinin
Hb	Hemoglobin
HCT	Hematocrit
HI	Hemagglutination inhibition
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IRB	Institutional Review Board
ITT	Intent-to-treat
ITTI	Intent-to-treat Infected
IV	Intravenous
IWRS	Interactive Web Response System
λ_z	Apparent terminal elimination rate constant
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
NA	Neuraminidase
NAb	Neutralizing antibodies
OTC	Over-the-counter
PK	Pharmacokinetic
PD	Pharmacodynamics
PT	Preferred term
QoL	Quality of Life
qPCR	Quantitative polymerase chain reaction
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure

SD	Standard deviation
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
t_{max}	Time of maximum concentration
US	United States
V_z	Apparent volume of distribution during the terminal elimination phase after intravenous dosing
WBC	White blood cell
WHO	World Health Organization

2.0 INTRODUCTION

2.1 Background Information

Influenza is an acute, contagious respiratory illness caused by viruses of the Orthomyxoviridae family. Influenza spreads around the world in seasonal epidemics. Symptoms range from mild to severe and generally include fever, sore throat, muscle pains, headache, tiredness, and cough. The disease is generally self-limiting: most people recover in less than 2 weeks. However, some groups of patients, notably the elderly, young children, pregnant women, and people with health conditions such as asthma, congestive heart failure, or a weakened immune system caused by disease or medication, have increased susceptibility to influenza-related complications. These can result in hospitalization and sometimes death. In Europe, recorded annual mortality from influenza in the 27 countries of the European Union (EU) ranged from 851 to 7,077 (EUROSTAT, the Statistical Office of the EU). In the United States (US), it has been estimated that influenza may cause approximately 3,000 to 49,000 deaths and result in approximately 200,000 hospitalizations.[1]

2.1.1 Treatment for Influenza

The two classes of antiviral drugs used against influenza are neuraminidase (NA) inhibitors (oseltamivir, zanamivir, and peramivir) and M2 protein inhibitors (amantadine derivatives). Neuraminidase inhibitors are currently preferred for flu infections as they are less toxic and more effective; however, they may be associated with the development of resistant virus strains.[2-5] There are currently no approved therapeutic biologics specifically for subjects with acute uncomplicated influenza A infection or serious and life-threatening complications of influenza A infections. To address this unmet medical need, CELLTRION (hereinafter referred to as the Sponsor) is developing CT-P27 for the treatment of influenza A.

2.1.2 Investigational Product

CT-P27 is a 1:1 mixture of two human Immunoglobulin G (IgG) 1 monoclonal antibodies, CT-P22 and CT-P23 that target an exogenous protein. These antibodies were selected from convalescent subjects and have been shown to neutralize influenza strains belonging to the H1N1 and H3N2 groups, as well as other potential pandemic clades like H2N2, H5N1, H7N9, and H9N2. CT-P27 drug product is believed to neutralize viral activity by binding to a conserved stem region of the viral HA protein, which is mediated through binding of the fusion peptide of virus HA to the endosomal membrane at low pH environment.

The CT-P27 antibody mixture was developed as a concentrate for dilution, to be administered by intravenous (IV) infusion in a clinical setting.

2.1.3 Non-Clinical Studies

[redacted]

2.1.4 Effects in Humans

[redacted]

2.1.4.1 Phase I Studies

[redacted]

2.1.4.2 Phase II Study

[redacted]

[redacted]

2.1.4.3 Efficacy in Humans

[redacted]

2.1.4.4 Safety in Humans

[redacted]

2.2 Rationale for Current Study

A previous Phase II study (Study CT-P27 2.1) demonstrated trends favoring the efficacy of low doses of CT-P27 on viral shedding measures and total symptom scores in healthy volunteers. The proposed Phase IIb study will 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. This study was designed to obtain an effect size of CT-P27 in comparison to placebo based on time to resolution of influenza symptoms and fever (see Section 8.1). Information on effect size, as

well as the safety, efficacy, and PK of CT-P27 at 45 mg/kg and 90 mg/kg will be used in the selection of doses in subsequent studies.

2.3 Hypothesis

The primary hypothesis is that time to resolution of influenza symptoms and fever is shorter in subjects receiving CT-P27 at 45 mg/kg and 90 mg/kg than in subjects receiving placebo.

2.4 Risk Assessment

2.4.1 Potential Risks and Risk Mitigation

Since CT-P27 is a mixture of two monoclonal antibodies, typical AEs of monoclonal antibody therapy might be expected.

However, the overall risks of allergic reactions posed by CT-P27 are expected to be low based on the type of product (i.e., monoclonal antibodies that target an exogenous protein). This expectation was supported by available non-clinical and clinical data as outlined above (also see the Investigator's Brochure).

Based on non-clinical data, free CT-P22 and CT-P23 are not expected to cause unwanted immune system activation via FcγRIIIa binding on effector immune system cells. Therefore, ADE is not expected. In the limited clinical experience with CT-P27, there were no anaphylactic reactions and only a few infusion-related TEAEs (headache, rash) were reported. Furthermore, the immunogenicity against CT-P27 components appeared to be extremely low.

To minimize the effects of an immune- or infusion-related reaction, study drug will be administered slowly, over a 90-minute period (±15 minutes). Emergency drugs and equipment suitable for assistance during anaphylactic reactions will be available during infusion with study drug.

[redacted]

This study will be performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulatory requirements.

2.4.2 Potential Benefits

There may be no direct benefit to the subjects participating in this trial. However, there is currently an unmet need for additional treatment options for influenza A. Therefore, the results of this study may assist in the development of a new treatment for influenza A.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to evaluate efficacy as determined according to the time to resolution of respiratory and constitutional symptoms of influenza and fever.

3.2 Secondary Objectives

The secondary objective is to evaluate the additional efficacy and safety of CT-P27, including potential effects on the incidence of antibody-dependent enhancement (ADE).

3.3 Exploratory Objectives

- To assess the pharmacokinetics (PK) of CT-P27 components (CT-P22 and CT-P23)
- To assess immunogenicity.
- To assess the characterization of isolated influenza viruses.

4.0 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

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). 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**.

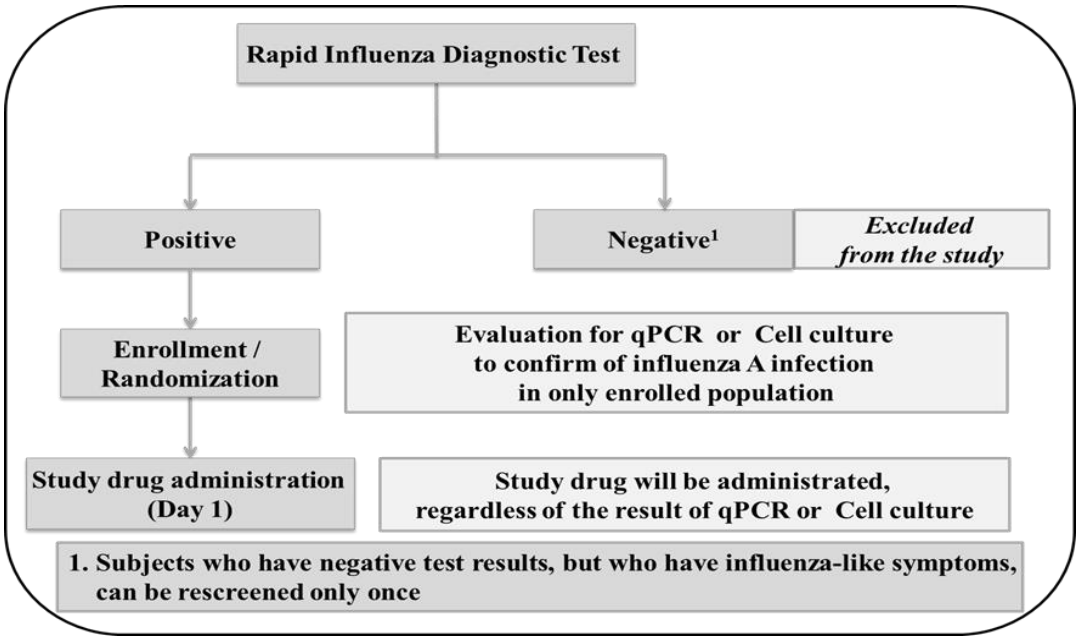


Figure 1 Enrollment Process

Approximately 183 subjects with influenza A to be enrolled in the study will be randomly assigned to 1 of 3 groups, 45 mg/kg CT-P27, 90 mg/kg CT-P27, 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 PK sub-study (Yes vs No). A schematic diagram of subject assignment is presented in **Figure 2**.

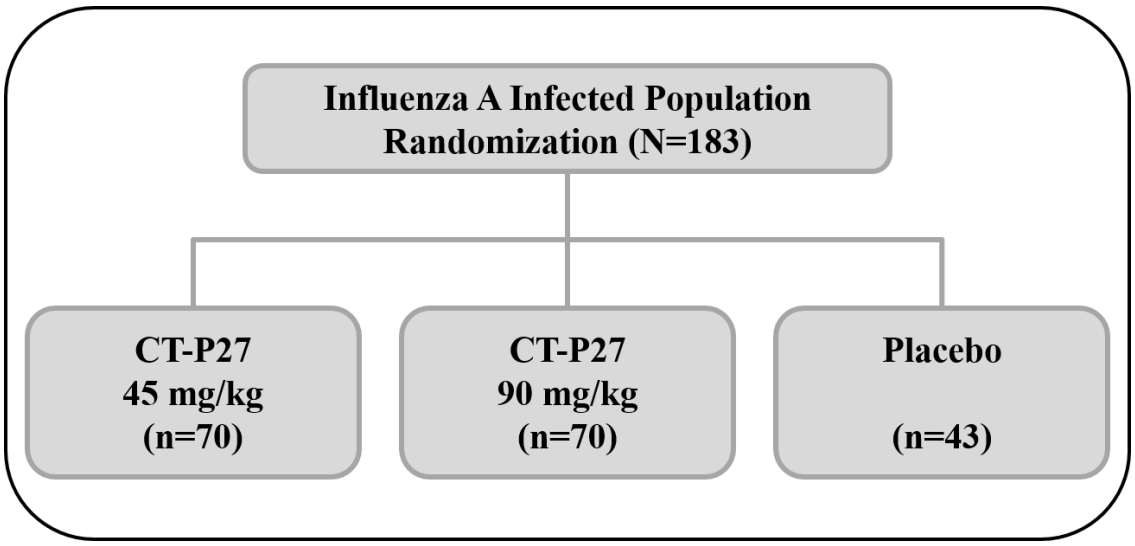
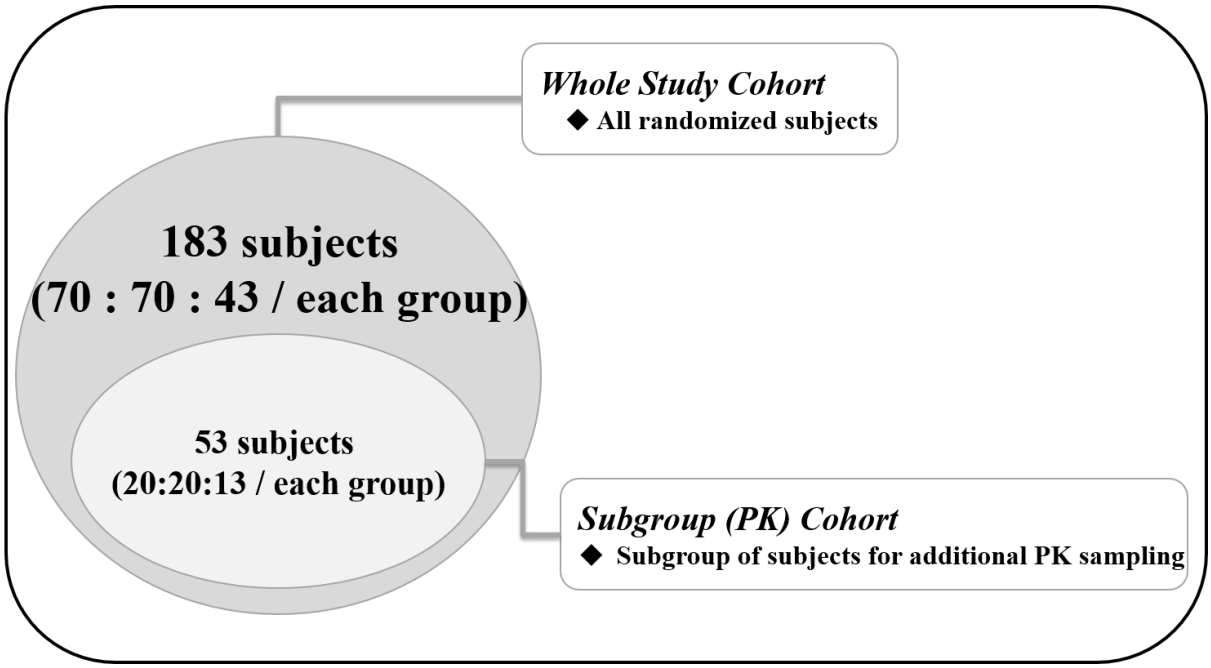


Figure 2 Schematic Diagram of Subject Assignment

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

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 in a hospital from Day 1 (before study drug administration) to Day 3 (after completion of the 48 hours assessments) if it is deemed necessary upon the judgement of the investigator.

Study visits:

- Subjects who are included in Whole Study Cohort and are hospitalized: 4 planned study visits
- Subjects who are included in Whole Study Cohort but are not hospitalized: 6 planned study visits
- Subjects who are included in the Subgroup (PK) Cohort and are hospitalized: 7 planned study visits
- Subjects who are included in the Subgroup (PK) Cohort but are not hospitalized: 9 planned study visits

Efficacy Assessment:

The completion of the Influenza Intensity and Impact Questionnaire (Flu-iiQ™) (see Appendix 2 for a copy of the questionnaire and Section 6.1.1.1 for details describing the questionnaire) and the recording of body temperature will take place at screening for baseline assessments. After study drug administration, subjects will be instructed to complete the Flu-iiQ™ and the body temperature in the diary 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]) and body temperature of subject will be also taken by site personnel at site at screening, Day 1 (prior to infusion), Day 2, Day 3, Day 5 and Day 8.
Nasopharyngeal swab samples will be used for viral shedding based on quantitative polymerase chain reaction (qPCR) and cell culture. Those samples will be taken at screening, 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), and Day 8 (168 hours [±4 hours] after the start of the study drug infusion). Laboratory confirmation of influenza A infection will be defined as a positive result by qPCR or cell culture.

Safety Assessment:

For safety evaluations, subjects will be followed up from the time the ICF is signed until Day 110 (approximately 5 half-lives) after the administration of study drug. Safety assessments will occur throughout the study.
Adverse events (AE) or concomitant medications that are verified by the investigator will be recorded on the eCRF. Up to Day 8, any AE or concomitant medication will also be recorded by subjects on their diaries and the investigators will refer to the records for information. If there is any AE or concomitant medication after Day 8, subjects will be instructed to contact the Principal Investigator or sub-Investigator at any time.
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.
Subjects with suspicious ADE will be required to assess virus titer using the nasopharyngeal swab sample, Flu-iiQ™ 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.

Exploratory Assessment:

Blood sampling for PK analysis will be collected from the subjects on:

- Day 1 at pre-infusion (within 15 minutes prior to the beginning of the infusion), the end of infusion (+15 minutes), 1 hour (±15 minutes) after the end of the 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),
- Days 29, 57 and 110 (±5 days) or at EOS visit

Blood sampling for Immunogenicity assessment will be collected on Day 1 (at pre-infusion) and Day 110 (±5 days) or EOS visit.

For the subjects with Influenza A confirmed by qPCR or cell culture, 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.

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. The Schedule of Assessments is presented in Table 1.

Table 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) [2]	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				
• 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)								

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)
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.
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.

4.2 Discussion of Study Design

This study uses a standard randomized, placebo-controlled study design. The study is designed to determine the effect size of two doses of CT-P27.

The selection of the study Cohort is appropriate for the evaluation of CT-P27 in subjects with acute, uncomplicated influenza A.

Placebo-controlled trials are appropriate in settings and Cohorts where the expected serious risk of non-treatment is small. For trials evaluating treatment of uncomplicated mild to moderate influenza, placebo-controlled rather than non-inferiority designs will be used because the risks associated with receiving placebo are low, and the efficacy of available treatment is modest (1 day difference in time to symptom improvement), variable, and cannot be predicted well enough to support an adequate non-inferiority margin. The variable clinical course of influenza in any given season, as well as the potential for differences in pathogenicity and host immunity as new influenza strains emerge and change over time, also makes uncontrolled data or historical controls difficult to interpret and inadequate to support efficacy of investigational drugs.

The doses were selected based on PK/PD modelling. The higher dose (90 mg/kg) was evaluated in a Phase I study. No significant adverse effects of treatment were observed.

The primary and secondary efficacy endpoints are consistent with the Food and Drug Administration (FDA) document, "*Guidance for Industry: Influenza: Developing Drugs for Treatment and/or Prophylaxis*" [6].

4.3 Selection of Study Cohort

Approximately 183 subjects will be enrolled (see Section 8.1). The study Cohort will consist of male and female subjects with acute uncomplicated influenza A who can be enrolled, screened, randomized, and treated with study drug no more than 48 hours following the onset of symptoms.

4.3.1 Inclusion Criteria

Each subject must meet all the following criteria to participate in this study:

1. Subject is a male or female and aged 19 to 64 years, inclusive.
2. Subject can voluntarily provide a written informed consent.

3. Onset of illness no more than 48 hours prior to the planned administration of study drug. If the adjustments of visit schedule is required, additional 12 hours can be allowed (Maximum onset of illness: 60 hours).

   Note: 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).

4. As reported by the subject and recorded on the Flu-iiQ™ completed at screening, the subject has at least two of the following symptoms (moderate to severe in intensity):

   a) Respiratory symptom (cough, sore throat, or nasal congestion) or
   b) Constitutional symptom (headache, feeling feverish, body aches and pains, or fatigue).

5. Subject has a fever ≥38.0°C or ≥100.4°F at screening or a history of fever within the 24 hours prior to screening and has received treatment with an antipyretic(s) in the 6 hours prior to screening.

6. Subject is diagnosed with influenza A at screening, using the Sponsor-supplied or agreed in advance rapid influenza diagnostic test. 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

7. For both male and female subjects, the subject and his/her partner (if of childbearing potential) agree to use a highly effective method of contraception during the study and for 5 months after the administration of study drug.

   a) Male and female subjects and their partner who have been surgically sterilized for less than 6 months prior to the date of informed consent must agree to use a highly effective method of contraception during the study and for 5 months after the administration of study drug.
   b) Menopausal females must have experienced their last menstrual period more than 12 months prior to the date of informed consent to be classified as not of childbearing potential.

8. Subject's body mass index (BMI) is of <35.0 kg/m^2 and weight is of ≤99.9 kg.

4.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Subject is not likely to complete all required study visits or procedures for any reason, in the opinion of the Investigator.
2. Subject has received a treatment with another investigational medical product or participated in another clinical trial within 30 days (or 5 half-lives, whichever is longer).
3. Subject has previous exposure to any anti-influenza monoclonal antibody therapy including CT-P27 prior to study drug administration.
4. Subject has a history of hypersensitivity to any monoclonal antibody or has a known hypersensitivity to any of the treatment components.
5. Subject is taking antiviral treatment for influenza (e.g., zanamivir, oseltamivir, rimantadine, amantadine, peramivir, or ribavirin) or has a history of using these antivirals within 14 days prior to the administration of study drug.
6. Subject has been immunized against influenza with live attenuated or inactivated virus vaccine within 21 days prior to the administration of study drug.
7. Subject has a medical condition including one or more of the following:
    a) Positive influenza B or influenza A+B infection.
    b) History or presence of congestive heart failure with symptoms consistent with New York Heart Association Class III or IV functional status within 12 months prior to study drug administration.
    c) Presence of clinically significant abnormality on a 12-lead ECG at screening that, in the Investigator's clinical judgment, may compromise the safety of the subject or affect the outcome of the study. These include, but are not limited to, a PR interval >200 msec, a corrected QT interval [QTc] >450 msec for male subjects and >470 msec for female subjects, or any evidence of heart block, right bundle branch block, or left bundle branch block.
    d) History or presence of any clinical condition or evidence of organ dysfunction that may affect either the subject’s ability to participate in the study or the study result, in the opinion of the Investigator.
    e) Subjects with abnormal liver function values. These will which include aspartate transaminase (AST), alanine transaminase (ALT) or alkaline phosphatase (ALP) ≥ 3 × ULN at screening.
    f) Subject with abnormal renal function values (serum creatinine ≥ 1.7 × ULN with creatinine clearance level ≤ 75mL/min at screening).
    g) In the opinion of the Investigator, the subject has active tuberculosis.

h) Uncontrolled diabetes mellitus (defined as known by the case of HbA1c >8%).

i) Uncontrolled hypertension (defined as known by the case of systolic blood pressure (SBP) ≥160 mmHg or diastolic blood pressure (DBP) ≥100 mmHg).

j) Documented, known current infection with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).

k) Severe infection within 30 days prior to the administration of study drug that required parenteral antibiotic use or hospitalization.

l) Any uncontrolled acute or chronic clinically significant respiratory disease (e.g., chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, asthma, or bacterial pneumonia).

m) History of malignancy within 2 years prior to study drug administration (with the exception of treated basal cell carcinoma of the skin or carcinoma in situ of the cervix) or current active malignancy.

8. Subject is currently hospitalized or currently requires hospitalization due to severity of illness, or has any plan for elective hospitalization within 1 month after study drug administration.

9. Subject requires oxygen therapy due to underlying disease or influenza infection.

10. Subject has a history of bone marrow or solid organ transplantation.

11. Subject uses systemic steroids or other immunosuppressant (except oral steroid up to 5-10 mg/day, methotrexate up to 10 mg/week).

12. Subject requires routine/intermittent hemodialysis or peritoneal dialysis.

13. Subject is pregnant or breastfeeding.

14. Subject is not eligible for the study participation for whatever reason (including clinical laboratory results) in the opinion of the Investigator, or shows evidence of a condition (psychological, emotional problems, any disorders or resultant therapy) that is likely to invalidate informed consent, or limited the ability of the subject to comply with the protocol requirements in the opinion of the Investigator, or unable to understand the protocol requirements, instructions and study related restrictions, the nature, scope and possible consequences of the clinical study, or is unable to give written informed consent or to comply fully with the protocol.

4.3.3 Disease Diagnostic Criteria

The subjects will be screened for the presence of influenza A using a rapid influenza diagnostic test no more than 24 hours before treatment with study drug. The presence of influenza A will

be confirmed with qPCR or cell culture in only enrolled subject. Subjects who are positive for influenza A on the rapid influenza diagnostic test but negative on qPCR or cell culture will continue in the study and be followed up for safety purposes.

4.3.4 Subject Withdrawal

All subjects are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. If a subject chooses to withdraw from the study, they will be encouraged to return to the site for safety reasons to complete the assessments planned for EOS visit

The Investigator will ensure that all reasonable attempts (telephone calls, contact with primary care physician, certified letter) are made to obtain follow-up safety information on subjects who do not return to the site for study visits or are lost to follow-up.

Subjects who are withdrawn from the study after randomization will not be replaced.

Subjects who withdraw from the study after dosing will be advised by the Investigator to continue contraception restrictions for 5 months after the administration of study drug.

The Investigator will ensure that the reasons for withdrawal are documented on the subject's medical records (source documents) and in the electronic Case Report Form (eCRF). If the subject withdraws due to an AE, the details of the AE must be entered on the AE section of the eCRF. If the reason for subject withdrawal is not known, the subject must be contacted and followed up in order to establish whether the reason for withdrawal was an AE, and if so, this must be reported in accordance with the procedures outlined in Section 6.2.1.5.

4.3.5 Study and Site Termination

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects.
- Enrollment is unsatisfactory.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

The Sponsor will notify the Investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment.
- Poor protocol adherence.
- Inaccurate or incomplete data recording.
- Non-compliance with the ICH guideline for GCP.

5.0 STUDY TREATMENTS

5.1 Treatments Administered

Subjects in this study will receive a single IV dose of the following:

- CT-P27 45 mg/kg
- CT-P27 90 mg/kg
- Placebo

An infusion solution of 0.9% w/v sodium chloride will be used for subject infusion. The bag will be gently inverted to mix the solution in order to avoid foaming. Parenteral solutions will be inspected visually for particulates and discoloration prior to administration and administration will not be performed if any particulates and discoloration are found. The detailed method about mixing the solution will be described in a guideline, which will be available at all site.

All study drugs will be administered as IV infusions over 90 minutes (±15 minutes).

5.2 Identity of Investigational Product(s)

Table 2 CT-P22 and CT-P23 Molecular Formula and Weight

	CT-P22	CT-P23
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

5.3 Packaging and Labelling

Investigational medicinal products will be packaged and labelled for each subject according to local legal requirements.

A label will be attached to the outside of each kit, as well as to the container. The text will be in compliance with local regulatory requirements and may include some of the following information:

- Protocol number
- Contents and quantity
- Lot number
- Kit number
- Directions for use
- Investigator's name
- Storage instructions
- Caution statement ("for clinical trial use only")
- Sponsor's contact name and address

- Expiry date

All supplies of CT-P27 must be stored at a refrigerated temperature between 2℃ and 8℃ . The temperature must be monitored. Until dispensed to the subjects, the CT-P27 will be stored in a securely locked area, accessible to authorized personnel only.

5.4 Precautions and/or Overdose

There are no specific antidotes to CT-P27. Treatment of an overdose should be symptomatic.

Subjects who develop severe infusion-related reactions must have infusion terminated immediately, and the subject will be treated according to the best standards of care. These subjects will be followed up until stabilized, or until the reaction resolves.

During infusion of study drug, emergency drugs and equipment suitable for assistance during anaphylactic reactions will be available during infusion with study drug.

5.5 Method of Assigning Subjects to Treatment Group

Once the subject has provided an informed consent and meets all the inclusion criteria and none of the exclusion criteria, the study site will request the study drug assignment using the Interactive Web Response System (IWRS).

All randomized subjects will be managed by IWRS. To randomize a subject, the study site will access the IWRS interlocking with electronic data capture system. The subject identifying information (e.g. gender, year of birth and/or date of birth) and the stratification factors are provided to gain the randomization number and investigational product allocation. Randomization information which includes randomization ID, regime name, regime ratio, date and time of randomization, and stratum name generated by IWRS will be delivered to the Sponsor.

5.6 Selection of Doses in the Study

Given the safety profile in clinical studies, and PK/PD modelling analysis using PK data from clinical and non-clinical studies, the efficacious doses for humans are expected to be in the range of 45 to 90 mg/kg.

5.7 Selection and Timing of Dose for Each Subject

All subjects will receive a single dose of study drug as randomized. As the study drug is administered at the study site, there are no specific instructions to be given to the subject as to how or when to take the study drug. It is critical that the infusion with study drug begins within 48 hours after the onset of influenza symptoms (window of +12 hours is allowed).

5.8 Blinding

The clinical trial will be performed in a double-blind manner. The study drug (CT-P27 and placebo) will be handled by a delegated unblinded pharmacist before the drug administration and will be administered by blinded personnel, with physically blind condition.

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 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.

5.8.1 Emergency Unblinding

Under normal circumstances, the blind will not be broken. The blind will be broken only if specific emergency treatment would be dictated by knowing the study drug status of the subject. The Investigator may, in an emergency, determine the identity of the study drug by using the applicable procedure in the IWRS.

The date, time, and reason for the unblinding must be documented in the appropriate field of the eCRF. The Sponsor and the Medical Monitor must be informed as soon as possible.

Suspected unexpected SAEs, which are subject to expedited reporting, will be unblinded before submission to the regulatory authorities, if required.

The overall randomization code will be broken only for reporting purposes. The unblinded analyses will be performed by the CRO or unblinded biostatisticians from the Sponsor. Only relevant CRO biostatisticians, medical writers, and the Sponsor will be unblinded at this stage. However, the subjects and investigators will remain blinded; all other study personnel will remain blinded until the end of the study. Final determination of the analysis sets will occur prior to finalizing the database for each analysis.

The randomization code will not be revealed to study subjects, parents or guardians, study site staff, or Investigators.

5.9 Prior and Concomitant Treatments

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.

The subjects will record concomitant medications in the subject diaries. Use of any medication during the study reported on the diary, reported to the Investigator, or prescribed by the Investigator will be transferred to the eCRF.

5.9.1 Prohibited Prior Medications

At screening, subjects with any of the following will be ineligible for enrollment.

- An investigational medical product in another clinical trial within 30 days (or 5 half-lives, whichever is longer) prior to study drug administration.
- A previous exposure to anti-influenza monoclonal antibody therapy.
- Previous antiviral treatment for influenza (e.g., zanamivir, oseltamivir, rimantadine, amantadine, peramivir, or ribavirin) at screening or has a history of using these antivirals within 14 days prior to study drug administration.
- Live attenuated or inactivated virus vaccine within 21 days prior to study drug administration.

5.9.2 Prohibited Concomitant Medication

The use of the following medication is prohibited from Day 1 until Day 110/EOS visit:

- Live attenuated or inactivated influenza vaccine.
- Systemic immunosuppressants.
- Other influenza anti-virals (such as amantadine, rimantadine, zanamivir, oseltamivir, peramivir, or ribavirin).
- Other investigational drugs.

5.9.3 Permitted Drugs

During the study, unless contraindicated, subjects may take acetaminophen/paracetamol, levodropropizine and chlorpheniramine for symptom relief according to the label's prescribing information and at dosages that do not exceed the manufacturer's recommendations. Those medication for symptom relief would be prescribed by investigators as P.R.N (pro re nata). The investigator should train the subject to administer maximum twice a day as much as possible. And administration of the medication during the study should be reported on the diary. Subject will be not allowed to use other drugs for symptom relief except acetaminophen/paracetamol, levodropropizine and chlorpheniramine.

If these drugs are taken, details concerning the dose and duration of treatment will be recorded in the subject's medical records (source documents) and in the eCRF.

5.10 Medical Care of Subjects after End of Study

The Sponsor will not provide any additional care to subjects after they leave the study. Subjects who require additional care will be encouraged to seek treatment from their personal physician.

5.11 Treatment Compliance

The Investigator or designee will administer/supervise the administration of study drug at the study site. Therefore, compliance will not be assessed as an outcome measure. The subject's date of treatment, dose, and duration of infusion will be recorded in the subject's medical records (source documents) and in the eCRF.

5.12 Study Drug Accountability, Dispensing and Destruction

It is the responsibility of the Investigator to ensure that all study drug received at the study site will be inventoried and accounted for throughout the study and the result recorded in the drug accountability form maintained at the study site. Contents of the study drug containers must not be combined. The drug accountability will be verified by the monitor during onsite monitoring visits. Study drug will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions.

The Investigator agrees not to supply the study drug to any person other than sub-Investigators, designated study site personnel, and the subjects participating in the study. Study drug may not be re-labelled or reassigned for use by other subjects unless approved by the Sponsor.

The Investigator will destroy empty or partially used vials as well as the cartons after reconstitution per site standard operating procedure, and keep tear-off labels for accountability. The Investigator agrees to neither dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the Sponsor. On a country-specific basis, permission may be granted for local disposition, with supporting documentation.

6.0 EFFICACY, SAFETY, EXPLORATORY PHARMACOKINETIC AND OTHER ASSESSMENTS

6.1 Efficacy Measures and Procedures

The methods used to obtain efficacy data are described below. Efficacy endpoints are discussed in Section 8.2.

The timing of each assessment and study procedure is presented in Table 1.

6.1.1 Diaries

Subjects will be issued a diary on Day 1 and will be required to record the diary from Day 1 to Day 8. The study site staff will instruct the subjects on the use of the diary. Subjects will be told to bring their completed diary each time they return to the study site. Study staff will review the entries in the diary (Flu-iiQ™ questionnaire, recording of body temperature, adverse event and concomitant medication). If the subject is not compliant in regard to filling out the diary (omissions, discrepancies, or other difficulties), instructions on how to use the diary may be repeated. Study site staff should encourage the subject to complete the diary and remind the subject of the importance of following study procedures while at home.

6.1.1.1 Flu-iiQ™

The Flu-iiQ™ is a validated questionnaire with four domains. These include the 1) intensity of influenza symptoms, 2) impact on activities, 3) effects on feelings and 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). Scores for influenza symptoms are none, mild, moderate, and severe.

The Flu-iiQ™ will be completed by subject at screening. After study drug administration, subjects will be instructed to complete the Flu-iiQ™ 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]).

The results of the first two domains of the Flu-iiQ™ (those assessing symptoms and the impact of influenza on activities) will be used in the assessment of primary and secondary efficacy endpoints (see Section 8.2). The results of the 3rd and 4th domain (impact on feelings and concerns) will be evaluated as QoL measures. A copy of the Flu-iiQ™ is included in Appendix 2. Information obtained from the diary will be transferred to the eCRF.

6.1.1.2 Body Temperature

The Sponsor will supply a thermometer to each subject along with directions for the use of the thermometer. Body temperature will be taken by subject 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)] and it will be taken by site personnel at site at screening, Day 1 (prior to infusion), Day 2, Day 3, Day 5 and Day 8.
These results will be recorded in the diary or source document at site and transferred to the eCRF.
Body temperature will also be taken at site visits as indicated in Table 1.

6.1.2 Nasopharyngeal Swabs

The Sponsor will provide nasopharyngeal swabs for use during the study. Samples from these swabs will be used to obtain samples for qPCR and cell culture, to confirm influenza A infection and evaluate viral shedding and to assess genotype, phenotype, and to assess antiviral resistance.

A nasopharyngeal swab sample will be obtained from all subjects and will be collected for two times to be used for rapid influenza diagnostic test and virology assessment at screening. Nasopharyngeal samples will be obtained at each subsequent study visit: 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), and Day 8 (168 hours [±4 hours] after the start of the study drug infusion).

The time selected for taking the swabs will be similar at each study visit (e.g., in the morning (between approximately 6 A.M. and 10 A.M.) or in the evening (between approximately 6 P.M. and 10 P.M.).

Under some circumstances additional nasopharyngeal swabbing may occur. If the subject meets the definition for suspicious ADE (see Section 6.2.5), the subject will have additional swabs taken (at scheduled or unscheduled visits, as necessary) until Day 8 (168 hours) after the day of ADE occurrence.

6.1.3 Rapid Influenza Diagnostic Testing

The Sponsor will supply the site a rapid influenza diagnostic test at screening to assess eligibility for the study. 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. Subjects who have negative test results, but who have influenza-like symptoms, can be rescreened only once. The diagnosis of influenza A will be confirmed by a positive qPCR or cell culture result.

Results of rapid diagnostic testing will be recorded on the eCRF.

6.1.4 Viral Shedding

Viral shedding will be determined using qPCR and cell culture; samples for these evaluations will be obtained from nasopharyngeal swabs taken during the study (see Section 6.1.2).

The methods for qPCR and cell culture will be described in a separate laboratory procedure manual.

The results obtained from the laboratory will be recorded in the virology laboratory database and transferred to the Sponsor.

6.1.5 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. Complications may include, but are not limited to, bacterial or other viral upper or lower respiratory tract infections, including otitis media, sinusitis, bronchitis, and pneumonia.

Secondary complications of influenza A infection will be considered as AEs or as adverse drug reactions based on the assessment of causal relationship with the study drug. If any of the secondary complications meet any of the SAE criteria, they will also be reported as SAEs. Secondary complications will be treated according to the local standard of care.

6.2 Safety Measures and Procedures

6.2.1 Definition of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject enrolled (i.e., when the ICF is signed) into this study regardless of its causal relationship to study drug. Subjects will be instructed to contact the Principal Investigator or sub-Investigator at any time after the ICF is signed if any symptoms develop.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease.

An AE includes a/an:

a) Exacerbation of a pre-existing condition or disease.

b) Increase in frequency or intensity of a pre-existing condition.

c) Condition first detected or diagnosed after informed consent.

d) Continuous persistent pre-existing disease or symptoms that worsen after the subject provides informed consent.

An AE does not include a/an:

a) Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE. Any complications of the procedure are also considered to be AEs.

b) Pre-existing disease or conditions present or detected at the start of the study that do not worsen.

c) Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic elective surgery, social and/or convenience admissions).

d) The disease or disorder being studied or signs or symptoms associated with the disease or disorder, unless more severe or frequent than expected for the subject's condition.

e) Overdose of either study drug or concurrent medication without any signs or symptoms.

Medical history and any medical conditions that are present prior to informed consent will be recorded as medical history and not be reported as an AE.

Any signs and symptoms of influenza A infection throughout the study, including the screening period, will be captured on the Flu-iiQ™ and the body temperature in the diary.

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. The clinically significant laboratory results include those that:

- Result in discontinuation from the study.
- Require treatment or any other therapeutic intervention.
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality).
- Are associated with clinical signs or symptoms judged by the Investigator to have a clinically significant impact.

6.2.1.1 Definition of Serious Adverse Event

A serious adverse event (SAE) is defined as any AE occurring at any dose that results in any of the following outcomes:

a) Death - the death was an outcome of an AE.

b) Life-threatening - the subject was at substantial risk of dying at the time of AE occurrence.

c) Inpatient hospitalization or prolongation of existing hospitalization.

d) A disability/incapacity - the AE resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the AE resulted in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life.

e) A congenital anomaly in the offspring of a subject who received drug - it is suspected that exposure to study drug prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

f) 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A distinction will be drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. An AE that is severe in intensity is not necessarily an SAE.

Clarifications:

- Any SAE that occurs after informed consent is signed will be reported.
- Life-threatening means that the subject is, in the view of the Investigator, at immediate risk of death from the event as it occurs. This definition does not include an event that, had it occurred in a more severe form, might have caused death.
- Hospitalization for elective treatment of a pre-existing condition that does not worsen during the study is not considered an AE.
- Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event is an SAE.
- Inpatient hospitalization means the subject has been formally admitted to a hospital for medical reasons (even if for less than 24 hours). However, this does not include the hospitalization due to the study treatment / procedure.
- Emergency room visit; the subject was seen and treated in the emergency room, and following treatment, subject was released. The Principle Investigator will assess if the event is considered a medically significant event.

6.2.1.2 Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., for applicable product information, include the Investigator's Brochure for an unapproved investigational product or the package insert/summary of product characteristics for an approved product). Therefore, if a treatment-related SAE occurs and it was not mentioned in the applicable product information, then it will be reported as a SUSAR (see Section 6.2.1.6).

6.2.1.3 Lack of Efficacy as an AE or SAE

Lack of efficacy is not considered as an AE in clinical trials. However, disease-related complications will be reported as an AE.

6.2.1.4 Evaluation of AEs

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

Seriousness

The event will be evaluated to determine if it meets the criteria for an SAE, as described in Section 6.2.1.1.

Severity/Intensity

The severity of the AE will be characterized according to the following criteria based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.03:

- 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 activities of daily living.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

When evaluating an AE that recurs over time (for example, a specific AE reported multiple times in the diary), the Investigator will review the AE for changes in severity over the time period being assessed. The most severe grade will be assigned to that AE.

Relationship/Causality

The Investigator will assess the causality/relationship between the study drug and the AE and record that assessment in the eCRF. One of the following categories will be selected based on medical judgment, considering the definition below and all contributing factors. However, for the summarization of data, all categories other than unrelated will be considered as related to study drug.

- Definite: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) will be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- Possible: The relationship suggests that the association of the AE with the study drug is unknown; however, the AE is not reasonably supported by other conditions.
- Probable: The relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a

causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression, or expression of disease state or concomitant medication reactions) do not appear to explain the AE.

- Unrelated: There is not a reasonable possibility that the study drug caused the AE.
- Not Assessable: All efforts will be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, (e.g., because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation).

6.2.1.5 Recording and Follow-up of AEs and SAEs

All AEs/SAEs, regardless of the relationship to study drug, will be assessed and recorded from the date the ICF is signed until Day 110 (approximately 5 half-lives) after the administration of study drug.

Subjects will be trained on the recording of AEs into their diary up to Day 8, and this information will be transferred to the eCRF after verification of the investigator. If there is any AE after Day 8, subjects will be instructed to contact the Principal Investigator or sub-Investigator at any time. Any AE occurring during the study must be documented in the subject's medical records, in accordance with the Investigator's normal clinical practice, and on the AE page of the eCRF. SAEs that occur during the study must be documented in the subject's medical record and on the SAE page of the eCRF. Serious adverse event reporting is discussed in Section 6.2.1.6.

A separate set of SAE pages will be used for each SAE. However, if at the time of initial reporting multiple SAEs that are temporally and/or clinically related are present, they may be reported on the same SAE page.

All AEs/SAEs will be recorded individually in the study subject's own words (verbatim) unless, in the opinion of the Investigator, the AEs/SAEs constitute components of a recognized condition, disease, or symptom. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE rather than the individual signs/symptoms.

If a clinically significant abnormal laboratory finding or other abnormal test result meets the definition of an AE or SAE, then the AE eCRF page or SAE eCRF page must be completed, as appropriate. A diagnosis (if known), or clinical signs and symptoms (if diagnosis is unknown), rather than the clinically significant abnormal laboratory finding or test result, will be entered on the AE or SAE eCRF page. If no diagnosis is known and clinical signs and symptoms are not present, then the abnormal finding will be recorded.

Treatment-related AEs and treatment-related SAEs will be followed up until resolution or medical condition stabilizes.

6.2.1.6 Reporting of a Serious Adverse Event and a SUSAR

Any SAE (including death due to any cause and SUSARs) that occurs during this study, whether or not related to the study drug, must be reported immediately (within 24 hours of the study site's knowledge of the event) by E-mail, telephone or fax to the Sponsor's authorized representative at the following table.

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The report will contain as much available information as possible concerning the SAE to enable the Sponsor (or an authorized representative) to file a report, which satisfies regulatory reporting requirements. If SAE follow up is reported via eCRF, a completed, separate SAE follow up notification should be sent to Sponsor (or CRO) by fax or email within 24 hours of the study site's awareness of the event.

The information in the report of the SAE must include at least the following:

- Name, address, and telephone number of the reporting Investigator.
- Investigational product and study code.
- Subject identification number, initials, sex, and date of birth or year of birth.
- Description of the AE/SAE, measures taken, and outcome.
- Preliminary classification of causal relationship by the Investigator.

If SAE follow up reporting is performed using a SAE report form, its original contents should be appropriately reflected on the relevant page of the eCRF.

Any SAEs reported spontaneously after the last study visit on Day 110 (or after EOS visit) will only be reported if the Investigator suspects a causal relationship to the study treatment.

6.2.1.7 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

Investigators will be notified by the Sponsor or designee of all SAEs that require prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Investigators will provide written documentation of IRB/IEC notification for each report to the Sponsor or CRO. The Sponsor or the designee will ensure that all SAEs are reported to the appropriate regulatory authorities.

Any SUSAR that is fatal or life-threatening must be reported to the appropriate national regulatory authorities and relevant ethics committees within 7 calendar days of awareness. Other SUSARs must be reported within 15 calendar days of awareness.

6.2.2 Contraception

The need to avoid pregnancy and a discussion concerning acceptable methods of contraception will be discussed with male subjects and female subjects of childbearing potential prior to the administration of study drug.

Menopausal females are not considered of childbearing potential if they have experienced their last period more than 12 months prior to the date of informed consent.

Both male and female subjects of childbearing potential and his/her partner will be required to use highly effective methods of contraception throughout the study and for 5 months after the administration of study drug. Highly effective methods of contraception include:

- Oral contraceptives.
- Other hormonal contraceptives administered as implants, percutaneous patches, or vaginal rings.
- Intrauterine devices.
- Double barrier methods, such as
    - Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository).
    - Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).
- Sterilization
    - Tubal ligation or vasectomy.

  Male and female subjects and their partners who have been surgically sterilized for less than 6 months prior to the date of informed consent must agree to use a highly effective method of contraception during the study and for 5 months after the administration of study drug.
- Abstinence from penile-vaginal intercourse, when this is the subject's preferred and usual lifestyle.

6.2.3 Pregnancy

Females of childbearing potential will have a pregnancy test performed at screening to ensure the exclusion of pregnant women from the study.

Female subjects will be instructed to inform the site if they become pregnant during the study. Male subjects will be instructed to inform the site if their partner becomes pregnant during the study.

Female subjects of childbearing potential will have an additional test for pregnancy at the end of the study (Day 110).

Any known or suspected pregnancy that occurs during the study either in subjects or female partners of male subjects must be reported to the Sponsor/designee within 24 hours of the time the Investigator becomes aware of the event. Suspected pregnancies in subjects will be confirmed with a pregnancy test. The subject will remain in the study and be monitored for safety.

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the study. The Investigator must follow up and document the course and the outcome of all pregnancies even if the subject withdraws consent or the study has finished.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of contraceptive medications or a suspected AE is associated with pregnancy.

Elective abortions without complications will not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn will not be considered an SAE.

All outcomes of pregnancy must be reported by the Investigator to the Sponsor on the pregnancy outcome report form within 30 days after he/she has gained knowledge of the normal delivery or elective abortion. The Investigator must follow up and document the course and the outcome of all pregnancies even if the subject was withdrawn from the study or if the study has finished. The baby will be followed for 1 year after the birth, provided consent is obtained; the Investigator must report any complications that occur even though the study has finished.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

6.2.4 Clinical Laboratory Evaluations

Urine samples will be collected and blood will be drawn from each subject at screening and on Day 3, and Day 8, as presented in Table 1. The clinical laboratory parameters evaluated in this study are presented in Table 3.

Clinical laboratory tests will be reviewed for results of potential clinical significance throughout the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, the abnormality will be reported as an AE (see Section 6.2.1 for definition of clinically significant laboratory results). Clinically significant laboratory results will be followed up to resolution or until the Investigator considers the abnormality chronic and/or the subject to be stable.

Urine pregnancy testing and all laboratory assessments will be done by a local laboratory.

Table 3 Clinical Laboratory Tests

Hematology: White blood cell count (WBC) with differential, including absolute neutrophil count Red blood cell (RBC) count Hematocrit (HCT) Hemoglobin (Hb) Platelet count Urinalysis: Color pH Specific gravity Ketones Protein Glucose Bilirubin Nitrite Urobilinogen Occult blood Microscopic examination of sediment Additional Tests (Screening only): Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis C virus antibody Human immunodeficiency virus (HIV)	Serum Chemistry: Albumin Alkaline phosphatase Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Blood urea nitrogen (BUN) Chloride Creatine kinase (CK) CK enzyme subtype* Troponin* Serum creatinine Creatinine clearance (estimated by weight and by Cockcroft-Gault formula) C-reactive protein Cholesterol Glucose Lactate dehydrogenase (LDH) Potassium Sodium Total bilirubin Direct bilirubin Total protein Uric acid Triglyceride Additional Tests (Screening and Day 110/EOS visit): Urine pregnancy (women of childbearing capacity) Serum pregnancy test Note: Urine pregnancy test will be performed before study drug administration in females of childbearing potential only. If the urine pregnancy test gives equivocal results, a serum pregnancy test will be performed to determine if the subject is pregnant. Pregnant women will be excluded from this study at screening.
*Relevant assessment for CK enzyme subtype and Troponin will be performed only when CK result shows a clinical significance.	

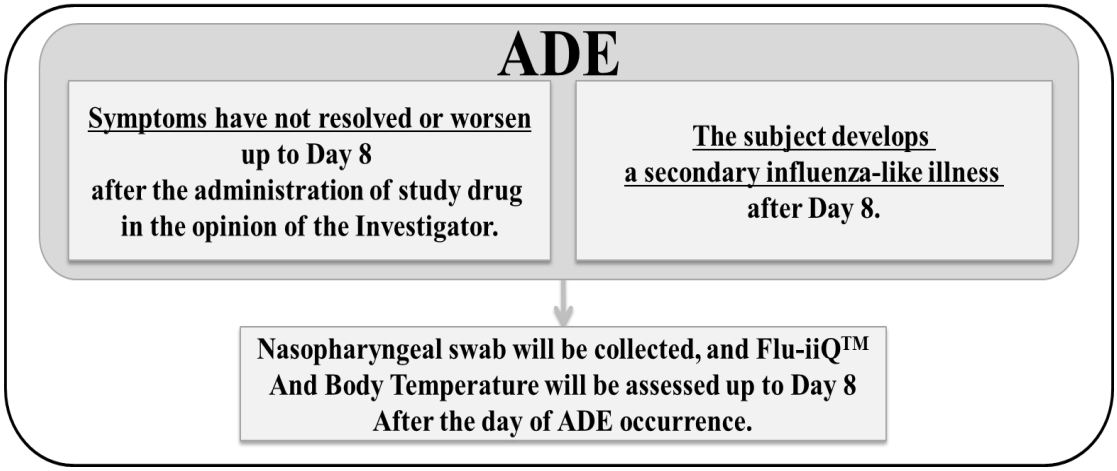
6.2.5 Antibody-dependent Enhancement

Subjects will be monitored for symptoms and levels of viral shedding suggestive of suspicious ADE throughout the study.

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.

Figure 4 Flow chart of Antibody-Dependent Enhancement (ADE)



If a subject meets any of the criteria for suspicious ADE, virus titer will be measured using nasopharyngeal swab samples collected at the time of occurrence, Day 2 (24 hours [±4 hours] after the day of ADE occurrence), Day 3 (48 hours [±4 hours] after the day of ADE occurrence), Day 5 (96 hours [±4 hours] after the day of ADE occurrence) and Day 8 (168 hours [±4 hours] after the day of ADE occurrence). Those subjects will need to record Flu-iiQ™ (influenza symptoms) and body temperature in their diary twice a day (at approximately 12-hour intervals) from the day of ADE occurrence to Day 8 (168 hours after the day of ADE occurrence): in the morning [between 6 and 10 AM, approximately] and in the evening [between 6 and 10 PM, approximately]. If symptoms have not resolved or have worsened up to Day 8 after the day of ADE occurrence, same procedures will repeat. In addition, genotypic analysis on HA and NA genes and phenotype characterization of potential escape variants with regard to CT-P27 will be performed.

If suspicious ADE occurs, DSMB will provide recommendations to continue or stop study after review of the case of suspicious ADE.

6.2.6 Vital Signs and Body Temperature

At site visits, vital sign measurements (systolic blood pressure [SBP], diastolic blood pressure [DBP], respiratory rate, and heart rate) and body temperature will be measured at the time points specified in Table 1. Blood pressure (sitting) and heart rate will be measured after the subject has rested (sitting quietly) for at least 5 minutes.

It should be noted that body temperature will also be recorded in on the eCRF, as discussed in Section 6.1.1.

6.2.7 Hypersensitivity Reactions

On Day 1, vital signs including blood pressure, heart rate and respiratory rate, body temperature, and ECG will be assessed at the following time points, 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 minute) after the end of the infusion.

Emergency drugs and equipment suitable for assistance during anaphylactic reactions will be available during infusion with study drug.

6.2.8 Physical Findings and Other Safety Assessments

A complete physical examination including examination of the head, neck, ears and throat, thorax, abdomen, extremities, neurological system, and skin and mucosae will be performed at screening and at Day 110/EOS visit. Evaluation of other body systems will only be performed when medically indicated in the opinion of the Investigator.

In addition, at each visit, the Investigator or designee will also perform a symptom-directed physical assessment (which should include, at a minimum, the examination of ear, nose, throat, sinuses, and lungs) and evaluation for potential complications of influenza.

Weight will be recorded at screening and at Day 110/EOS visit. Height will be recorded at screening, only.

Twelve-lead ECGs will be performed at screening, on Day 8 (±4 hours), and Day 110 (±5 days)/EOS visit.

Electrocardiogram recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. The Investigator or designee will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered by the Investigator to be clinically significant.

Chest x-ray will be performed to assess respiratory infection at screening, and whenever needed during the study, as determined by the Investigator.

All results will be recorded in the appropriate sections of the eCRF.

6.3 Exploratory Assessments

A PK sub-study will only be performed on the subjects who signed additional informed consent to participate in a PK sub-study. Blood sampling for PK analysis will be collected from subjects on Day 1 at pre-infusion (within 15 minutes prior to the beginning of the infusion), the end of infusion (within 15 minutes after the end of the infusion), 1 hour (±15 minutes) after the end of the infusion, and then on 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.

Samples taken on Day 1 will be collected in the opposite arm from that being used for the IV infusion of study drug. The date and time of collection of each sample and any missing blood draws will be recorded in the respective eCRF. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

Bioanalysis will be carried out for the simultaneous determination of CT-P22 and CT-P23 using a validated ligand binding assay. Bioanalysis will be carried out at the bioanalytical site. Contact details for the bioanalytical site are available in Table 4.

Blood will be drawn at Day 1 (before study drug administration) and Day 110/EOS visit to evaluate the immunogenicity of CT-P27 components, CT-P22 and CT-P23. Samples will be secured at the central laboratory for immunogenicity analysis and backup samples will be retained.

For the subjects with Influenza A confirmed by qPCR or cell culture, genotypic analysis on HA and NA genes, and phenotype characterization of potential escape variants with regard to CT-P27 will be evaluated using the nasopharyngeal swab samples. Samples will be secured at the central laboratory for analysis and backup samples will be retained.

In addition, blood samples will be taken at Day 1 (at pre-infusion) and Day 29 (±5 days)/EOS visit (if a subject is early terminated from the study) to determine HI antibody in Subgroup (PK) Cohort.

Primary samples will be secured at the central laboratory for PK, immunogenicity of CT-P22 and CT-P23, and HI antibody analysis and backup samples will be retained. Back-up samples will be retained up to 5 years after the end of the study unless a specific authorization is

given by the sponsor to destroy the back-up sample. Primary and back-up samples will be shipped to the central laboratory according to the laboratory manual, and primary samples should be shipped separately from the back-up samples.

6.4 Demographics and Medical History

At screening, information on demographics and background characteristics will be collected. The demographics include age, sex (male or female), and race (Caucasian, African, Asian, or Other). A general medical history (e.g., previous illnesses, current conditions, and family history, smoking habits) will also be collected. In addition, medical history of a subject can be newly added on the eCRF at any time point during the AE assessment period. 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 date of the event occurs before the ICF is signed. If a pre-existing medical event or condition recorded as medical history worsens after the ICF is signed, it would be reported as an AE, even if the onset date was prior to signing ICF.

The information will be recorded on the eCRF.

6.5 Appropriateness of Measurements

The primary and secondary efficacy endpoints are consistent with the "Guidance for Industry: Influenza: Developing Drugs for Treatment and/or Prophylaxis" provided by the FDA. The Flu-iiQ™ used in this study is a validated questionnaire developed to evaluate the influenza symptoms.

The primary virology outcome, quantitative changes in viral shedding, is assessed using standard qPCR and cell culture methods.

7.0 QUALITY CONTROL AND QUALITY ASSURANCE

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel before the study, periodic monitoring visits by the Sponsor or its designee, and direct transmission of clinical laboratory data from a local laboratory into the clinical database. The eCRF will be reviewed for accuracy and completeness by the monitor during on-site monitoring visits and after their return to the Sponsor or its designee; any discrepancies will be resolved with the Investigator or designees, as appropriate. The data will be entered into the study database and verified for accuracy.

Quality assurance personnel from the Sponsor or its designee may visit the study site to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the eCRF. Subject privacy must, however, be respected. Sufficient prior notice will be provided to allow the Investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a licensing application. The Investigator will immediately notify the Sponsor or its designee if they have been contacted by a regulatory agency concerning an upcoming inspection.

7.1 Data Management/Coding

Electronic Data Capture (EDC) will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study site. Data collection will be completed by authorized study site staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study site staff prior to the study being initiated and any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs will always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort will be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable, or unknown, the Investigator will indicate this in the eCRF. The Investigator will be required to electronically sign-off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies

between critical data. All entries, corrections, and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study site staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff and time and date stamp are captured.

The eCRF is essentially considered a data entry form and will not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who receives study drug, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, will be clearly identified with the study and subject number. Any personal information, including subject name, will be removed or rendered illegible to preserve individual confidentiality.

The eCRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction will be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events and medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA); concomitant medication will be coded using the World Health Organization (WHO) Drug Dictionary. The version numbers for both dictionaries will be presented in the Statistical Analysis Plan (SAP).

7.2 Quality Assurance Audit

Study sites, the study database, and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or designee. In addition, inspections may be conducted by regulatory bodies at their discretion.

The Investigator will promptly notify the Sponsor and designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports/certificates received to the Sponsor.

8.0 STATISTICS

The complete version of the SAP will include all detailed statistical analysis methods, which will be available after the each Data Review Meeting. This statistical section presented below summarizes the SAP.

The first analysis of data will occur after all subjects have completed the assessments scheduled for Day 15. These data will be used to determine the efficacy of treatment with CT-P27 to establish an effect size for subsequent clinical studies. The data will also provide information about the safety and PK (only Subgroup [PK] Cohort) of CT-P27 up to Day 15. An additional analysis will be performed when all subjects have completed the assessments scheduled for Day 110/EOS visit.

8.1 Determination of Sample Size

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 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 standard deviation (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.

8.2 Study Endpoints

8.2.1 Primary Efficacy Endpoints

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

Resolution of symptoms has occurred if the following influenza symptoms (as recorded on the Flu-iiQ™) 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 <37.0ºC for at least 24 hours.

8.2.2 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 (<37.0ºC) for at least 24 hours.
- Time to resolution of individual symptoms for at least 24 hours as recorded on the Flu-iiQ™.
- Severity of symptoms as recorded on 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™.

8.2.3 Secondary Safety Endpoints

The following safety parameters are secondary endpoints:

- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious adverse events (TESAEs)
- TEAEs leading to treatment discontinuation
- Clinical laboratory analyses (hematology, biochemistry, and urinalysis laboratory tests)
- Vital sign measurements
- ECGs
- Physical examination findings

- Evaluation of ADE throughout the entire study duration. For the definition of suspicious ADE, please see Section 6.2.5.

8.2.4 Exploratory Endpoints

Blood sampling for PK analysis will be collected from the subjects on:

- Day 1 at pre-infusion (within 15 minutes prior to the beginning of the infusion), the end of infusion (+15 minutes), 1 hour (±15 minutes) after the end of the 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), Days 29, 57 and 110 (±5 days) or at end of study visit (EOS visit).

Blood sampling for Immunogenicity assessment will be collected on Day 1(at pre-infusion) and Day 110 (± 5days) or EOS visit.

For the subjects with Influenza A confirmed by qPCR or cell culture, genotypic analysis on HA and NA genes, and phenotype characterization of potential escape variants with regard to CT-P27 will be evaluated using the nasopharyngeal swab samples.

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.

Additional genotyping tests could be conducted if it is required from a regulatory or medical perspective.

The following parameters are determined as 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

- Anti-drug specific antibodies for CT-P27 component antibodies (CT-P22 and CT-P23)
- HI antibody.
- Genotype and phenotype of isolated influenza virus

8.3 Statistical Methods

The statistical analysis will be performed using [redacted]. The statistical methods for this study, summarized in the following, will be described in a detailed SAP, which will be finalized prior to locking of the database and unblinding of the treatment codes. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the final study report.

The data documented and the clinical parameters measured in this study will be described using descriptive statistics (including number [n], mean, median, SD, minimum, and maximum) for quantitative variables and frequency counts and percentages for qualitative variables. Data will be listed in data listings.

Baseline will be the latest available measurement prior to the start of the infusion of study drug.

Pharmacokinetic parameters will be computed by non-compartmental methods [redacted].

8.4 Analysis Populations

8.4.1 Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all subjects randomized to study drug or placebo. All subjects will be included in the ITT as randomized even if they do not receive treatment. The secondary efficacy endpoint analysis and all baseline and demographic summaries will be performed on the ITT population.

8.4.2 Intent-to-Treat Infected Population

The intent-to-treat infected (ITTI) population is defined as all randomized subjects with confirmed influenza A by qPCR or cell culture. The primary and secondary efficacy endpoint analysis, the genotype and phenotype analysis will all be performed on the ITTI population.

8.4.3 Safety Population

The safety population is defined as all randomized subjects receiving any amount of placebo or CT-P27. All safety and immunogenicity analyses will be based on the safety population.

8.4.4 Pharmacokinetic Population

The PK population is defined as approximately 53 subjects (20 per CT-P27 treatment groups and 13 in placebo group) in Subgroup (PK) Cohort and 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. All PK analyses will be based on the PK population.

If infusion interruptions and/or infusion rate adjustments occur during 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 infusion duration will be longer than 90 minutes (±15 minutes) in these cases and this will be documented in the eCRF.

In addition, HI antibody, and the subject baseline characteristics analysis will all be performed on the PK population.

8.5 Statistical Analyses

8.5.1 Primary Efficacy Analysis

The primary efficacy endpoint analysis will assess the time (in days) from the administration of study drug to resolution of influenza symptoms and fever. This analysis will be performed on the ITTI population. Data will be obtained from responses recorded on the Flu-iiQ™.

Resolution of symptoms has occurred if the following influenza symptoms (as recorded on the Flu-iiQ™) 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 <37.0ºC for at least 24 hours. (The start time for resolution of fever is defined as the time recorded in the diary when body temperature was <37.0ºC for at least 24 hours.)

If the subject has received the drugs for symptom relief, the effective duration of the drugs for symptom relief should be considered.

For example, the study drug was administered at 12:00 on 1st day. The first time body temperature recorded <37.0ºC 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 <37.0ºC], it will be calculated that the start time point for body temperature <37.0ºC is 15:00 on 2nd day [27 hours after the study drug administration]. Then, if the next first time body temperature recorded <37.0ºC in the diary was 22:00 on 2nd day and body temperature was <37.0ºC 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].

The primary efficacy endpoint will be analyzed using a Wilcoxon rank-sum test to assess differences between treatment groups, if every subject were followed until resolution of influenza symptoms and fever. The statistically significant difference of time to resolution of influenza symptoms and fever between placebo and CT-P27 based on Wilcoxon rank-sum test will be presented by p-values. If there is any censoring, the primary efficacy endpoint will be analyzed using Log-rank test, and Kaplan-Meier plots will be presented.

8.5.2 Secondary Efficacy Analyses

The secondary efficacy endpoints will be analyzed on the ITTI and ITT populations.

Time (in days) to resumption of normal activity, return to normal body temperature (<37.0ºC), and resolution of individual symptoms will be analyzed using a Kaplan Meier model to assess differences between placebo and CT-P27.

Individual symptoms and total symptom score will be summarized by severity, by time point, and by treatment group.

Viral shedding (titers) based on qPCR and cell culture will be evaluated at the scheduled collection times. Changes in viral shedding will be assessed as the change from baseline in qPCR and $\log_{10}$ $TCID_{50}$/mL.

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

The number and percentage of subjects with secondary complications of influenza will be summarized by treatment group.

Results for questions included in the remaining domains (3 and 4) (effect on feelings, effect on concerns) of the Flu-iiQ™ will be summarized by collection time and treatment group.

Scheduled selection times are presented in Table 1.

8.5.3 Exploratory Analyses

Pharmacokinetics 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, median, minimum, maximum, geometric mean, and coefficient of variation (CV%). All PK analyses will be based on the PK population. Dose proportionality for CT-P22 and CT-P23 will be assessed. Details are provided below.

Serum concentrations will be summarized by treatment group at each scheduled collection time as specified in Table 1. In addition to the standard summary statistics (n, mean, SD, median, minimum, and maximum), the geometric mean and CV% will also be presented at each time point. 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 and scheduled and actual sample times will be presented in data listings by treatment. Individual linear and semi-logarithmic concentration-time plots (based on scheduled sample times) with respective treatments presented together will also be included. For the calculation of PK parameters, all serum concentrations that are below the limit of quantitation (BLQ) prior to the first measurable concentration will be set to zero. The BLQ values after administration of study drug will be set equal to the lower limit of quantification.

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

- $AUC_{0\text{-last}}$ calculated using the linear trapezoidal rule. This will be calculated over the study period.
- C_{max} obtained directly from the observed concentration versus time data.
- $AUC_{0\text{-}\infty}$ 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} obtained directly from the observed concentration versus time data.
- C_{last} obtained from the last observed quantifiable concentration.

- λ_z 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.
- $t_{½}$ determined as $\ln 2/\lambda_z$.
- MRT, determined as $AUMC_{0-\infty}/AUC_{0-\infty}$, where $AUMC_{0-\infty}$ is the area under the first-moment curve evaluated from time zero to infinite time.
- CL calculated as the administered dose divided by $AUC_{0-\infty}$.
- V_z calculated as Dose/($\lambda_z \cdot AUC_{0-\infty}$), 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	The time interval (hour) 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 will be listed and not summarized if Rsq is less than 0.800.
$\%AUC_{ex}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC_{0-\infty}\times 100]$. If the extrapolated area (C_{last}/λ_z) is greater than 30% of $AUC_{0-\infty}$, then $AUC_{0-\infty}$ and related parameters will be listed and not summarized.

For the calculation of PK parameters, pre-dose samples that are BLQ or missing will be assigned a numerical value of zero for the calculation of the AUC. 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 summarized by treatment group. Summary statistics will include n, mean, SD, median, minimum, maximum, geometric mean, CV%.

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) or P-value for the slope will be presented.

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. These data will be summarized by treatment groups and time point.

Genotype and phenotype analysis will be assessed in the ITTI population by baseline and post-treatment virus measures.

In addition, changes in HI antibody will be assessed in the PK population and summarized by treatment group and time point.

8.5.4 Safety Analyses

The safety analysis will be performed on the safety population at the time points specified in Table 1 by presenting data on TEAEs, TESAEs, TEAEs leading to treatment discontinuation, clinical laboratory analyses, vital signs, ECG, physical examination, suspicious ADE, and other safety evaluations.

8.5.4.1 Adverse Events

Adverse events will be graded for severity and the terminology of AEs will be described according to the CTCAE v4.03. All safety data will be listed and summarized by treatment group as appropriate.

Adverse events will be coded to system organ class (SOC) and preferred term (PT) according to MedDRA.

The following TEAE summaries will be reported by SOC, PT, and treatment group:

- Number and percentage of subjects reporting at least one TEAE by SOC and PT
- Number and percentage of subjects reporting at least one TESAE by SOC and PT
- Number and percentage of subjects reporting at least one TEAE leading to treatment discontinuation by SOC and PT

Treatment-emergent AEs will also be summarized by maximum severity and relationship to study drug with the percentage of subjects in each category. If more than one TEAE is recorded for a subject within any SOC or PT, the subject will only be counted once using the most severe assessment.

The number and percentage of subjects with suspicious TEADE will be presented by treatment group.

8.5.4.2 Clinical Laboratory Evaluations

Clinical laboratory tests (hematology, biochemistry, and urinalysis) will be summarized, by treatment, at each scheduled collection time. For continuous parameters, change from baseline will also be summarized for all scheduled collection times after the first infusion. Clinical laboratory data will also be summarized using shift tables for categorical parameters.

All laboratory results will be listed.

8.5.4.3 Vital Signs Measurements, Physical Findings, and Other Safety Evaluations

Vital signs of SBP, DBP, heart rate, and respiration rate will be summarized by treatment group, at each scheduled collection time. Changes from baseline will also be summarized by treatment group.

The number and percentage of subjects with abnormalities in vital signs or ECG during the infusion and immediate post-infusion period will be summarized by time point and treatment group.

Physical examination results will be summarized by counts and percentages at each scheduled collection time. In addition, shift tables will be presented.

Electrocardiogram parameters will be summarized by counts and percentages, at each scheduled collection time. In addition, shift tables will be presented.

8.5.5 Subject Baseline Characteristics

Demographics (age, sex, and race) and other background characteristics such as medical history will be presented in summary tables for the ITT population and ITTI population. Qualitative data will be summarized in contingency tables, and quantitative data will be summarized using quantitative descriptive statistics.

8.6 Data to be Analyzed

The data will be inspected for inconsistencies by performing validation checks.

All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the SAP before database lock.

8.6.1 Missing Data

Missing data from subjects who withdraw from the study, including AEs and any follow-up, will be included in the primary endpoint analysis in the ITTI population. Assuming Missing at Random (MAR), multiple imputation will be the primary imputation method for handling the missing data. Sensitivity analysis using tipping point analysis under Missing Not at Random (MNAR) will be also accessed for the primary endpoint analysis in the ITTI population.

8.7 Interim Analyses

There is no interim analysis planned.

9.0 ETHICS

9.1 Institutional Review Board or Independent Ethics Committee

An Ethics Committee will approve the final protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The Investigator will provide the Sponsor or CRO with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the study site(s). The Investigator will submit the written approval to the Sponsor or representative before enrollment of any subject into the study.

The Sponsor or representative will approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to the Sponsor or CRO of required IRB/IEC's annual renewal of the protocol and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the ethics committee with a brief report of the outcome of the study, if required.

The Sponsor or representative will provide Regulatory Authorities, Ethics Committees, and Investigators with safety updates/reports according to local requirements, including SUSARs, where relevant.

9.2 Ethical Conduct of the Study

This study will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013)[7], the applicable guidelines for GCP (CPMP/ICH/135/95), or the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. The study will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety, and well-being of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

9.3 Subject Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The ICF contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug. The Investigator will provide each subject with a copy of the signed and dated consent form.

10.0 STUDY ADMINISTRATION

10.1 Administrative Structure

Table 4 Administrative Structure

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

10.2 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study site will plan on retaining such documents for approximately 15 years after study completion. The study site will retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records.

For studies conducted outside the US under a US Investigational New Drug Application (IND), the Principal Investigator must comply with US FDA IND regulations and with those of the relevant national and local health authorities.

10.3 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject randomized into the study.

The Investigator will allow the Sponsor, the CRO, and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual subject medical records, as appropriate.

10.4 Investigator Information

10.4.1 Investigator Obligations

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP (GCP, 1996 [8]); the US CFR Title 21 parts 50, 54, 56, and 312; and European Legislation; and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator agrees to conduct the study in compliance with this protocol after the approval of the protocol by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

10.4.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 1). By signing the protocol, the Investigator confirms in writing that he/she has read, understands, and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for Good Clinical Practice [8] and applicable regulatory requirements. The study will not be able to start at any site where the Investigator has not signed the protocol.

10.4.3 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available.

Independent analysis and/or publication of these data by the Investigator or any member of his/her staff are not permitted without prior written consent of the Sponsor. Written permission to the Investigator will be contingent on the review by the Sponsor of the statistical analysis and manuscript and will provide for nondisclosure of the Sponsor's confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties 60 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to

other parties. The publication policy with respect to the Investigator and study site will be set forth in details in the Clinical Trial Agreement.

10.5 Financing and Insurance

The Sponsor will obtain liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

11.0 STUDY MANAGEMENT

11.1 Monitoring

11.1.1 Data Safety Monitoring Board

This study will be monitored by an independent DSMB consisting of a PK specialist, statistician, chairing physician, and an independent physician. Further details will be provided in a DSMB charter.

11.1.2 Monitoring of the Study

The Sponsor has engaged the services of a CRO to perform all monitoring functions within this study. Study monitors will work in accordance with the CRO's SOPs and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study site, informing the Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, monitors will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also control adherence to the protocol at the study site. They will arrange for the supply of investigational product and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each site while subjects are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion that contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, entries in the eCRFs will be compared with the original source documents (source data verification). For all entries, 100% of the data will be checked.

11.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or other regulatory agency access to all study records.

The principal investigator or sub-investigator should promptly notify the sponsor and its designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports or certificate received to the sponsor.

The investigator should promptly notify the sponsor and CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted to the investigator's IRB/IEC for approval before subjects can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to regulatory regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Deviations from the protocol, including deviations of inclusion/exclusion criteria, will be assessed as "minor" or "major" in agreement with the sponsor. Deviations will be defined prior to unblinding. Principal investigators will be notified in writing by the

monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

11.3 Study Termination

Although CELLTRION, Inc. has every intention of completing the study, CELLTRION, Inc. reserves the right to discontinue the study at any time for clinical or administrative reasons.

Study termination is defined as the date on which the last subject completes the last visit (if the study is not discontinued by CELLTRION, Inc.).

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and Content of Clinical Study Reports.

It is planned that 2 clinical study reports will be written.

12.0 REFERENCES

1. Centers for Disease Control and Prevention. *Seasonal Influenza Q & A.* http://www.cdc.gov/flu/about/qa/disease.htm.

2. Hsu J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP, Cheung A, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Ann Intern Med 2012; 156(7):512-24.

3. Pizzorno A, Abed Y, Boivin G. Influenza drug resistance. Semin Respir Crit Care Med 2011; 32(4):409-22.

4. Smith SM, Gums JG. Antivirals for influenza: strategies for use in pediatrics. Paediatr Drugs. 2010; 12(5):285-99.

5. Smith JR, Rayner CR, Donner B, Wollenhaupt M, Klumpp K, Dutkowski R. Oseltamivir in seasonal, pandemic, and avian influenza: a comprehensive review of 10-years clinical experience. Adv Ther. 2011; 28(11):927-59.

6. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) April 2011 *Clinical Antimicrobial Guidance for Industry Influenza: Developing Drugs for Treatment and/or Prophylaxis* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm091219.pdf

7. World Medical Association *Declaration of Helsinki*. *Ethical Principles for Medical Research Involving Human Subjects.* (Oct 2013) http://www.up.ac.za/media/shared/Legacy/sitefiles/file/45/2875/declarationofhelsinki_fortaleza_brazil2013.pdf

8. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use ICH Harmonised Tripartite Guideline, *Guideline for Good Clinical Practice E6(R1)* 10 June 1996. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

13.0 APPENDICES

13.1 Appendix 1: Signature of Investigator

PROTOCOL 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: CT-P27 2.2

This protocol is a confidential communication of CELLTRION. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from CELLTRION.

I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to subjects. I agree to administer the investigational medicinal product only to subjects under my personal supervision or the supervision of a Coordinating Investigator.

I will not supply the investigational medicinal product to any person not authorised to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the site in which the study will be conducted. Return the signed copy to CELLTRION.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Site: _____

_____

_____

13.2 Appendix 2: Flu-iiQ™

[Note: It is the Sponsor's responsibility to obtain copyright permissions for any scales or questionnaires]