Study Protocol

Title: A Phase 1, Randomized, Double-Blind, Single Ascending Dose Study to Determine the Safety, Tolerability, and Pharmacokinetics of CD388 Subcutaneous Administration in Healthy Japanese Subjects

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PROTOCOL TITLE PAGE

Title	A Phase 1, Randomized, Double-Blind, Single Ascending Dose Study to Determine the Safety, Tolerability, and Pharmacokinetics of CD388 Subcutaneous Administration in Healthy Japanese Subjects
Study Drug	CD388 Injection
Original Protocol	09AUG2022
Amendment 1	12DEC2022
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Confidentiality Statement:

PROTOCOL APPROVAL PAGE

Protocol: CD388.SQ.1.03

A Phase 1, Randomized, Double-Blind, Single Ascending Dose Study to Determine the Safety, Tolerability, and Pharmacokinetics of CD388 Subcutaneous Administration in Healthy Japanese Subjects

Original Protocol: 09AUG2022

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SPONSOR SIGNATURE

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14-Dec-2022

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Taylor Sandison, MD, MPH

Chief Medical Officer
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1. PROTOCOL SYNOPSIS

Sponsor: Cidara Therapeutics Inc., San Diego, CA

Product Name: CD388 Injection

Active Ingredients: CD388

Protocol Title: A Phase 1, Randomized, Double-Blind, Single Ascending Dose Study to Determine the Safety, Tolerability, and Pharmacokinetics of CD388 Subcutaneous Administration in Healthy Japanese Subjects

Planned Study Centers: Single center in the United States

Phase of Development: 1

Indication: Influenza virus infection

IND Number: 155,536

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the safety and tolerability profile of CD388 Injection when dosed by subcutaneous (SQ) administration as a single dose to healthy Japanese adult subjects.	• Incidence and severity of treatment-emergent adverse events (TEAEs), including but not limited to adverse events (AEs) and serious adverse events (SAEs) (including systemic reactogenicity/ injection site reactions and hypersensitivity reactions), AEs leading to study drug discontinuation and/or study withdrawal, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory tests (including hematology, coagulation, serum chemistry, and urinalysis), after a single dose of CD388.
Secondary	
• To determine the plasma pharmacokinetic (PK) profile of CD388 Injection when dosed by SQ administration as a single dose to healthy Japanese adult subjects.	• Pharmacokinetic parameters following CD388 Injection administration: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{½}$), apparent clearance (CL/F), apparent volume of distribution (V_Z/F), area under the plasma concentration-time curve from time 0 to time of last quantifiable sample ($AUC_{0\text{-last}}$), area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$).
Exploratory	
• To evaluate the PK profile of CD388 in upper respiratory tract after SQ administration as a single dose to healthy Japanese adult subjects.	• Pharmacokinetic parameters following CD388 Injection administration: maximum nasopharyngeal (NP) concentration (C_{max}), time to maximum NP concentration (T_{max}), area under the NP concentration-time curve from time 0 to time of last quantifiable sample ($AUC_{0\text{-last}}$).

Objectives	Endpoints
Exploratory (continued)	
• To evaluate biomarkers that may be associated with safety, reactogenicity, and immunogenicity after CD388 Injection.	• Results of the analyses of exploratory biomarkers (including but not limited to cytokines, chemokines, acute phase reactants, etc.).
• To evaluate CD388 immunogenicity.	• Anti-drug antibody (ADA) titers in blood (plasma or serum).
• To explore the effect of CD388 Injection on the occurrence of influenza-like illness (during flu season).	• Occurrence of influenza-like illness reporting during the outpatient follow-up period.

Study Design

This is a Phase 1, single-center, prospective, randomized, double-blind study of ascending single doses of CD388 Injection administered SQ to healthy Japanese adult subjects. The goals are to assess safety, tolerability, and PK of CD388.

Subjects will be randomized to receive a single dose of CD388 or placebo administered via SQ injection (treatment assignment is blinded) according to the design in the table below.

	Number of Subjects (N = 27)	
Cohort: dose	**CD388 (n = 21)**	**Placebo (n = 6)**
Cohort 1: 50 mg	7	2
Cohort 2: 150 mg	7	2
Cohort 3: 450 mg	7	2

Note: A subject may not receive treatment in more than one cohort.

After 50% of Cohort 1 subjects have completed study drug administration and have undergone protocol-specified procedures and assessments for ≥10 days, the Principal Investigator (PI) and Sponsor will review blinded safety data: AEs (including systemic reactogenicity/injection site reactions, hypersensitivity reactions, and adverse events of special interest [AESIs]), vital signs, 12-lead ECGs, and clinical laboratory results (hematology, coagulation, serum chemistry, urinalysis) to determine the safety and tolerability of the study drug. The incidence and severity of AEs, and any adverse changes in vital signs, clinical laboratory findings, and ECGs will be considered when determining safety and tolerability of study drug. If the dose is determined to be safe and well tolerated ≥10 days after dosing, Cohort 2 will be enrolled. Enrollment of the remaining 50% of Cohort 1 will continue while the safety data of the first 50% of Cohort 1 is being reviewed. Similar processes will be followed for dose escalation from Cohort 2 to Cohort 3.

The Schedule of Events is presented in Table 1. All subjects will be admitted to the clinical research unit (CRU) for observation and safety assessments from Day -1 (check-in) to Day 14. Subjects will be monitored for AEs (including systemic reactogenicity/injection site reactions, hypersensitivity reactions and AESIs) and SAEs throughout the study until the final study visit after dosing. Safety will also be assessed by physical examinations, ECGs, vital signs measurements, and laboratory evaluations (hematology, coagulation, serum chemistry, urinalysis) at various time points during and after the CRU stay. Concomitant medication use will be recorded throughout the study.

Blood samples for PK and ADA assessments will be collected throughout the study. To maintain the blind, samples will be collected from all subjects; however, only samples from the CD388 Injection group will be analyzed (using validated assays) by an unblinded central bioanalytical laboratory. Additional blood samples will be collected for pharmacogenomics and exploratory biomarker evaluation.

Respiratory tract infection (RTI) surveillance will be conducted during the outpatient phase of the study from CRU discharge through the Day 120/165 outpatient visit or a lab-confirmed influenza infection, whichever occurs first. Subjects will be provided nasal/throat swab kits (for detection of influenza infection or other respiratory pathogen by a multiplexed polymerase chain reaction [PCR] test) and symptom diary cards.

If 3 or more RTI symptoms listed in the table below occur (at least one must be a respiratory symptom), subjects will contact study staff, then collect nasal/throat swab samples (the swabs should take place as soon as possible after the start of symptoms, ideally within 48 hours, but no later than 5 days). Subjects will complete symptom diary cards every 7 days to capture the worst grade of symptoms that occurred during the previous week. The Investigator/study staff will arrange for prompt shipment of the nasal/throat samples to the testing laboratory. Note: If the reported symptoms are already of a level of severity that urgent care is indicated, the subject should be directed to the appropriate facility to receive this care (e.g., emergency room). Otherwise, symptoms should be treated according to standard of care.

If an influenza infection is confirmed by the testing laboratory before the Day 120/165 outpatient visit, the event should be documented until all symptoms have resolved, including completion of the symptom diary card every 7 days. Thereafter, no further RTI surveillance will be carried out on the subject.

If the nasal/throat swab samples are not confirmed to be influenza by the testing laboratory, diary card completion will continue through the Day 120/165 outpatient visit.

Respiratory Tract Infection (RTI) Symptoms	
• Runny nose (rhinorrhea)	• Shortness of breath (dyspnea)
• Stuffy nose (nasal congestion)	• Wheeze
• Sore throat	• Chilliness/feverishness or temperature ≥100°F
• Earache	• Headache
• Cough	• Body ache
• Productive phlegm/sputum	

As part of the surveillance, subjects will be questioned during all outpatient site visits for RTI symptoms. If the interval to the next outpatient site visit exceeds 15 days, subjects will be contacted by the Investigator/study staff every 2 weeks to query for RTI symptoms. Subjects should be reminded to contact the Investigator/study staff if RTI symptoms occur, and to collect the nasal/throat swab samples and complete the symptom diary cards every 7 days.

Number of Subjects

A total of 27 subjects will be enrolled in this study; 21 to receive CD388 Injection and 6 to receive placebo.

Inclusion Criteria

Subjects must meet ALL the following inclusion criteria:

1. Must be of Japanese descent with Japanese parents and grandparents, as determined by subject's verbal report.
2. Willing and able to provide written informed consent.
3. Males and females 18 to 65 years of age, inclusive.
4. A female subject must meet one of the following criteria:
   a. If of childbearing potential – agrees to use a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) for at least 30 days prior to screening and agrees to remain on a highly effective method until 7 months after last dose of study medication. Examples of highly-effective methods of contraception are located in Appendix 1.
   b. If a female of non-childbearing potential – should be surgically sterile (i.e., has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation/occlusion without reversal surgery) or in

a menopausal state (at least 1 year without menses), as confirmed by follicle-stimulating hormone (FSH) levels (≥40 mIU/mL).

5. A woman of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin) at screening and a negative urine pregnancy test on Day -1 before the first dose of study drug.
6. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of at least 7 months after study drug administration.
7. A male subject that engages in sexual activity that has the risk of pregnancy must agree to use a double barrier method (e.g., condom and spermicide) and agree not to donate sperm during the study and for at least 7 months after the last dose of the study medication.
8. Good health and without signs or symptoms of current illness.
9. Normal clinical examination, including:
   a. No physical examination findings that an Investigator determines would interfere with interpretation of study results.
   b. Screening ECG without clinically significant abnormalities (see Appendix 2).
   c. Creatinine clearance (CrCL) ≥80 mL/min as calculated using the Cockcroft-Gault equation:

$$CrCL = \frac{(140 - age) \times (weight\ in\ kg)}{72 \times (serum\ creatinine\ in\ mg/dL)} \times (0.85\ if\ female)$$

   d. Negative urine screen for drugs of abuse and alcohol at screening and Day -1.
10. Body weight ≥50 kg and body mass index between 18.0 and 30.0 kg/m^2, inclusive, using the following equation:

$$BMI = \frac{(weight\ in\ kg)}{(height\ in\ meters)^2}$$

11. Willing to refrain from strenuous physical activity that could cause muscle aches or injury, including contact sports, at any time from screening through 30 days after any dose of study drug.
12. Subject has adequate venous access for blood collection.

Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria:

1. History of any hypersensitivity or allergic reaction to zanamivir or other neuraminidase inhibitors (i.e., laninamivir, oseltamivir, peramivir), or to excipients of the CD388 Injection drug formulation; or history of drug-induced exfoliative skin disorders (e.g., Stevens-Johnson syndrome [SJS], erythema multiforme, or toxic epidermal necrolysis [TEN]).
2. History of any of the following:
   a. Allergies, anaphylaxis, skin rashes (foods such as milk, eggs, medications, vaccines, polyethylene glycol [PEG], etc.).
   b. Chronic immune-mediated disease, positive first-degree family history of autoimmune diseases.
   c. Atopic dermatitis or psoriasis.
   d. Bleeding disorder.
   e. Psychiatric condition, seizures, hallucinations, anxiety, depression, or treatment for mental conditions.
   f. Migraines.
   g. Syncope, or vasovagal syndrome with injections or blood draws.
   h. Cardiac arrythmia considered clinically significant by the Investigator.
3. Subjects with one or more of the following laboratory abnormalities at screening as defined by the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events v2.1 (DAIDS 2017):
   a. Serum creatinine, Grade ≥1 (≥1.1 × upper limit of normal [ULN]).
   b. Pancreatic amylase or lipase, Grade ≥2 (≥1.5 × ULN).

c. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT), Grade ≥1 (≥1.25 × ULN).
d. Total bilirubin, Grade ≥1 (≥1.1 × ULN).
e. Any other toxicity Grade ≥2, except for Grade 2 elevations of triglycerides, low density lipoprotein cholesterol, and/or total cholesterol.
f. Any other laboratory abnormality considered to be clinically significant by the Investigator.

Note: Retesting of abnormal laboratory values that may lead to exclusion will be allowed once without prior asking approval from the Sponsor. Retesting will take place during a scheduled or unscheduled visit during screening. Subjects with a normal value at retest may be included.

4. Alcohol or drug addiction in the past 2 years.
5. Experiencing symptoms of acute illness or chronic disease within 14 days prior to clinical research unit (CRU) check-in.
6. At screening, a positive result for hepatitis B virus surface antigen, hepatitis C virus antibody, or human immunodeficiency virus (HIV) antibody.
7. A positive result at CRU check-in for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by polymerase chain reaction (PCR).
8. Unwilling to comply with local health policy effective at the time regarding coronavirus disease 2019 (COVID-19). Full COVID-19 vaccination prior to participation is strongly recommended.
9. Women who are pregnant or nursing.
10. Received any over-the-counter (OTC) medications or nutritional supplements within 7 days, or any prescription medications within 14 days or <5 half-lives prior to dosing, whichever is longest (except for hormonal contraceptives, acetaminophen, or ibuprofen).
11. Current nicotine user or has quit habitual nicotine use in the 30 days prior to screening.
12. Received any vaccines or immunoglobulins within 28 days prior to dosing (90 days in case of intravenous immunoglobulin [IVIg] or biologics, or 14 days for COVID-19 vaccine).
13. Donated blood (within 56 days of screening) or plasma (within 7 days of screening) or experienced significant blood loss or significant blood draw (blood donation or blood loss of ≥500 mL) when participating in non-interventional clinical trials within 30 days prior to dosing.
14. Received a blood transfusion within 28 days prior to dosing.
15. Received any biologics within 90 days prior to dosing; or previous participation in another study (including investigational device studies) within 30 days of dosing or 5 half-lives of the study drug, whichever is longer, prior to screening (prior participation at any time in non-invasive methodology trials in which no drugs were given is acceptable).
16. Previous treatment with CD388.
17. Preplanned surgery at any time during the study.
18. The Principal Investigator (PI) considers that the volunteer should not participate in the study.

Test Product, Dose and Mode of Administration

CD388 Injection is a clear to lightly opalescent liquid essentially free of particulate matter containing the active pharmaceutical ingredient, CD388. CD388 Injection is supplied as a frozen sterile solution in single-use vials.

CD388 Injection is administered by subcutaneous (SQ) injection at 50 mg, 150 mg, or 450 mg (Cohort 1, Cohort 2, or Cohort 3, respectively). Dose levels to be assessed will follow an ascending single-dose regimen with the starting dose based on findings from 3-month rat and monkey toxicology studies.

Comparator

Normal saline will be administered SQ as the placebo control.

Duration of Treatment

A single dose of study drug will be administered SQ on Day 1. Study participation will require up to 28 days for screening procedures, and ~120/165 days for dosing and follow-up (check-in to the CRU on Day -1; CRU inpatient stay for study drug administration, observation, and assessments and procedures for 15 days [Days -1 to Day 14]; and 5 CRU outpatient visits for additional assessments and procedures).

Criteria for Evaluation

Safety and Tolerability of Study Drug

Safety and tolerability will be assessed by monitoring AEs (including systemic reactogenicity/injection site reactions, hypersensitivity reactions, and AESIs), vital signs, 12-lead ECGs, clinical laboratory results (hematology, coagulation, serum chemistry, urinalysis), and concomitant medication usage throughout the study.

See the Study Design section for details regarding cohort/dose level enrollment timing and assessment of safety and tolerability for dose escalation decision.

If a dose level is considered not safe or well tolerated, the study drug assignment for the subject(s) with the safety issue may be unblinded. The Sponsor may also independently decide to unblind the entire cohort for safety concerns or terminate enrollment for any reason.

If any subject develops a Grade ≥2 AE or an SAE of any grade that is deemed related to the study drug, the mechanism of the AE may be assessed (i.e., cytokine level, complement activation, immunoglobulin G [IgG] subtypes, immunoglobulin E [IgE], T-cell/B-cell/monocyte and basophil activation as assessed by flow cytometry, ADA development, and immune complex formation) at Sponsor and Investigator discretion, and the study dose may be modified for the remainder of the study.

Pharmacokinetics/Anti-drug Antibodies

Pharmacokinetics will be determined by analyzing plasma samples for concentration of CD388 obtained from subjects who receive CD388 Injection in each cohort at various time points after administration of study drug. Anti-drug antibodies (ADA) will also be measured at selected time points by a validated enzyme-linked immunosorbent assay (ELISA) method.

Pharmacogenomics

A mandatory pharmacogenomic (DNA) blood sample will be collected once, preferably on Day 1 (collection at another time point is permitted if necessary) to allow for genetic research to help understand the characteristics of CD388. Genetic analysis will be conducted if it is hypothesized that this may help explore genetic markers that could explain differences in safety, immunogenicity, or clinical response among subjects. Host DNA assessment will be limited to research related to CD388, including the development of tests/assays related to CD388 and flu-like disease.

Analyses of host DNA may be conducted at the Sponsor's discretion and reported separately from the study report.

Exploratory Biomarkers

Blood samples will be collected to allow for the exploration of biomarkers on the assumption that these markers could play a role in the response (safety, reactogenicity, immunogenicity) to CD388.

These samples and remaining material from other samples may be used for further assay optimization/ qualification, biomarkers, or further exploratory analyses. Samples will only be used for research related to influenza virus infection, flu-like disease, and safety, reactogenicity, and immunogenicity of CD388, including the development of tests/assays related to CD388 and influenza.

Analyses of biomarkers may be conducted at the Sponsor's discretion and reported separately from the study report.

Withdrawal from Study

Subjects may be withdrawn from the study for any of the following reasons:

- Subject is unable or unwilling to continue
- Subject elects to withdraw informed consent
- Adverse event (whether or not related to study drug) that precludes further participation in the study in the judgment of an Investigator and/or Sponsor
- Protocol non-compliance
- Subject lost to follow-up, or follow-up is not possible
- The Investigator considers that it is in the subject's best interest not to continue participation in the study

If a subject is removed from the study for any reason, the subject will be followed for resolution of any ongoing AE(s).

Temporary Study Halt for Safety Review

The study will be temporarily halted, pending review of available data, if any of the following occur:

- If ≥2 subjects experience the same Grade 3 AE event or laboratory abnormality within 28 days after study drug administration, considered attributable to CD388 or cannot be attributed to another cause
- If ≥1 subject experiences a Grade 4 AE or laboratory abnormality within 28 days after study drug administration, considered attributable to CD388 or cannot be attributed to another cause
- If ≥1 subject experiences an SAE irrespective of toxicity grade within 28 days after study drug administration, considered attributable to CD388 or cannot be attributed to another cause

If it is considered appropriate to restart the study following an internal safety review, an amendment, if required, will be submitted to the Food and Drug Administration (FDA) and Institutional Review Board (IRB). The study will not restart until the amendment has been approved by the FDA and IRB.

Statistical Methods

Safety, tolerability, and PK will be summarized using descriptive statistics. There will be no formal hypothesis testing. Analysis populations are:

- Safety Population: all subjects who receive any amount of study drug
- PK Analysis Population: all subjects who receive CD388 Injection and who have any blood samples analyzed

A Statistical Analysis Plan (SAP) will be prepared and finalized before unblinding for the first interim analysis. Any deviations from the final SAP will be described and justified in the study report. All statistical analyses will be performed using SAS®.

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables, will be provided. All data will be summarized separately by dose level and study drug (CD388 Injection or placebo). Listings of individual subject data will also be produced.

Safety will be evaluated by presenting summaries of AEs and SAEs, ECGs, clinical laboratory evaluations (hematology, coagulation, serum chemistry, urinalysis), and vital signs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs and AESIs will be presented by System Organ Class (SOC) and Preferred Term (PT), relationship to study drug, and severity. A TEAE is defined as an AE that emerges during or after study drug administration having been absent pre-treatment, or worsens relative to the pre-treatment state, and through the final study visit. In addition, the incidence of serious TEAEs and TEAEs leading to discontinuation of study drug or from the study will be presented by SOC and PT. Descriptive statistics for clinical laboratory test results, ECG parameters, and vital signs, and for changes from Baseline, will be presented by time point. The incidences of potentially clinically significant (PCS) clinical laboratory results, ECG parameters, and vital signs will also be summarized by time point.

A summary of the injection site evaluation will be presented. The number and percentage of subjects with any local reaction will be provided, as will the number and percentage of subjects with pain, tenderness, erythema/redness, and induration/swelling. The severity of each local reaction will also be presented.

The number and percentage of subjects with any RTI will be provided.

The PK parameters that will be assessed in the PK Analysis Population include:

- maximum plasma concentration (C_{max})
- time to maximum plasma concentration (T_{max})
- terminal elimination half-life ($t_{½}$)
- apparent clearance (CL/F)
- apparent volume of distribution (V_Z/F)
- area under the plasma concentration-time curve from time 0 to time of last quantifiable sample ($AUC_{0\text{-last}}$)
- area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$)

Analysis of the ADA results is to be determined and may include determination of the subject's positive/negative ADA status at baseline, treatment-emergent ADA in subjects with a negative baseline, as well as a post-baseline increase in titer for subjects with positive ADA at baseline.

1.1. Schedule of Events

Table 1: Schedule of Events

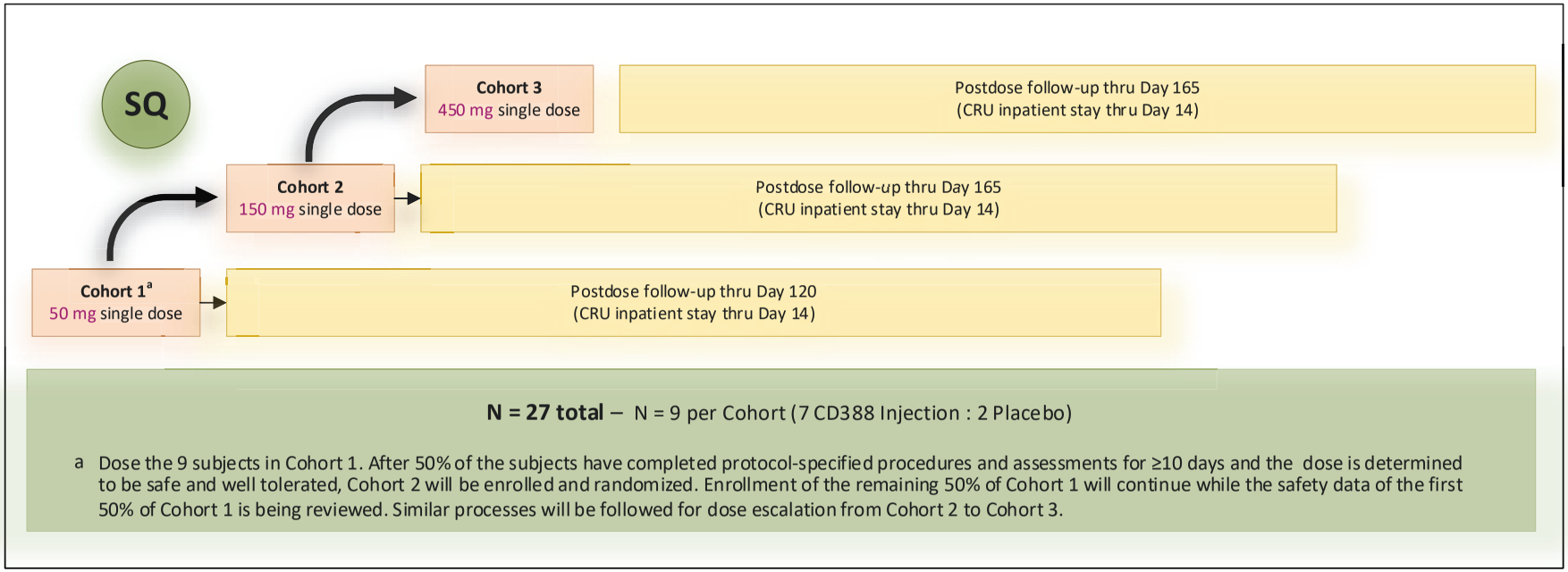
	Screening	Clinical Research Unit (CRU) Inpatient Stay								Outpatient CRU Visits				
Day (Window)	**-28 to -2**	**-1**	**1**	**2**	**3–6**	**7**	**9**	**11**	**14**	**30 (±3)**	**45 (±3)**	**60 (±5)**	**90 (±7)**	**120/165 [a] (±14)**
Informed consent	X													
Inclusion/Exclusion criteria	X	X												
Medical history/demographics	X													
Complete physical with vital signs (BP, RR, HR, oral temperature, height, weight, BMI)	X													
Targeted physical with vital signs (BP, RR, HR, oral temperature, weight [b])		X	X [c]	X	X	X			X	X	X	X	X	X
Safety ECG [d]	X	X	X			X			X	X				X
Laboratory evaluations (CBC with platelets, coagulation, serum chemistry, lipids, urinalysis)	X	X		X	X [e]	X			X	X	X	X	X	X
Virology screening (HBV, HCV, HIV)	X													
Virology screening (SARS-CoV-2)		X												
Serum/urine pregnancy test [f]	X	X								X		X	X	X
FSH (if applicable to confirm postmenopausal status)	X													
Drug/alcohol screen [g]	X	X												
Randomization			X											
Dosing of study drug			X											
Reactogenicity/injection site inspection [h]			X	X	X									
PK sample collection [i]			X	X	X	X	X	X	X	X	X	X	X	X
Pharmacogenomics blood sample [j]			predose											
Exploratory biomarker samples			predose		X [e]									
Anti-drug antibodies			predose						X	X	X	X	X	X
Nasopharyngeal swab collection [k]			predose	X	X	X	X	X	X	X				
Assess and record AEs [l]	←													→
Concomitant medications/procedures review [m]	←													→

Abbreviations: AEs = adverse events; BMI = body mass index; BP = blood pressure, CBC = complete blood count; COVID-19 = coronavirus disease 2019; CRU = clinical research unit; DAR = drug-antibody ratio; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; hr = hour; ICF = informed consent form; PK = pharmacokinetic; RR = respiration rate; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Schedule of Events (continued)

a. The timing of this visit is Day 120 for Cohort 1 and Day 165 for Cohorts 2 and 3. For subjects who discontinue study early, the Day 120/165 procedures should be performed.
b. Weight should be measured at each of the outpatient visits (Days 30, 45, 60, 90, 120/165).
c. On Day 1, the targeted physical examination should be performed predose. Vital signs collection will occur predose, 6 hours postdose, and as clinically indicated, and will be measured with the subject in a seated position for at least 3 minutes prior to measurement.
d. A triplicate 12-lead ECG is to be performed at screening, at CRU check-in on Day -1, predose (immediately prior to study drug administration) and 6 hours postdose (±10 minutes) on Day 1, and as indicated in the schedule. Subjects are to be resting (at least 5 minutes) and semi-recumbent when ECG is being conducted.
e. Laboratory evaluations (including exploratory biomarker samples) need to be performed once during the Day 3–6 interval on Day 4.
f. A sensitive serum pregnancy test (β-human chorionic gonadotropin) is required at screening and Day 120/165 for females of childbearing potential. Urine pregnancy test may be performed at all other time points.
g. Drug and alcohol screen is to be performed during the outpatient visits if vital signs are abnormal (see Appendix 2).
h. At indicated visits, inspection of administration site and surrounding area will be performed twice daily (once between approximately 2–4 hours postdose, and once approximately 8–12 hours postdose, then twice daily on other indicated study days at least 6 hours apart), with any abnormal findings reported as AEs. Reactions will be rated according to the scale provided in Table 5.
i. Blood samples for PK analysis will be collected predose (-24 hour window); post-dose at 2, 4, and 12 hours (each ±10 minute window); 24 hours (±30 minute window); 48 hours (±1 hour window); 72, 96, 120 hours (each ±2 hour window); and in the morning on Days 7, 9, 11, 14. Postdose samples collected at outpatient CRU visits at Days 30, 45, 60, 90, and 120/165 have the same windows (i.e., in ±days) as the visits.
j. A mandatory pharmacogenomic (DNA) blood sample will be collected once, preferably on Day 1 (collection at another time point is allowed if necessary) to allow for pharmacogenomic research related to CD388.
k. Nasopharyngeal swab samples will be collected predose on Day 1, and on Days 2, 5, 7, 9, 11, 14, and 30.
l. Adverse events (including influenza-like illness which will be tested for both COVID-19 and flu) will be collected for all subjects from the time of signing the ICF through the final study visit.
m. Concomitant medication and procedures, including those used to treat an AE, will be recorded from 28 days prior to the CD388 Injection/placebo administration until the final study visit.

1.2. Study Schema



2. TABLE OF CONTENTS

2.1. LIST OF TABLES

3. LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0–last}$	area under the plasma (or nasopharyngeal) concentration-time curve from time 0 to time of last quantifiable sample
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 extrapolated to infinity
BMI	body mass index
BSA	body surface area
CDC	US Centers for Disease Control and Prevention
CL/F	apparent clearance
C_{max}	maximum plasma (or nasopharyngeal) concentration
COVID-19	coronavirus disease 2019
CrCL	creatinine clearance
CRU	clinical research unit
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
Fc	crystallizable fragment
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgE	immunoglobulin E

Abbreviation	Definition
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IRB	Institutional Review Board
IVIg	intravenous immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
NA	neuraminidase
NAI	neuraminidase inhibitor
NCA	non-compartmental analysis
NOAEL	no-observed-adverse-effect level
NP	nasopharyngeal
OTC	over-the-counter
PCR	polymerase chain reaction
PCS	potentially clinically significant
PEG	polyethylene glycol
PI	Principal Investigator
PK	pharmacokinetic(s)
PT	Preferred Term
RBC	red blood cell(s)
RTI	respiratory tract infection
SAE	serious adverse event
SAER	Serious Adverse Event Report
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SJS	Stevens-Johnson syndrome
SOC	System Organ Class
SOP	Standard Operating Procedure
SQ	subcutaneous
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TM	targeting molecule
T_{max}	time to maximum plasma (or nasopharyngeal) concentration

Abbreviation	Definition
ULN	upper limit of normal
US	United States
V_Z/F	apparent volume of distribution
WBC	white blood cell(s)

4. BACKGROUND AND RATIONALE

4.1. Background

4.1.1. Influenza – Prevention and Treatment

Globally, millions are hospitalized each year and about 650,000 deaths occur due to influenza (Iuliano 2018). In the United States (US), an estimated 37–43 million influenza-related illnesses, 17–20 million influenza-related medical visits, 500,000 to 650,000 influenza-related hospitalizations, and 61,000 deaths occurred during the 2018–2019 influenza season (Brammer 2019). These numbers remain high year after year because currently no effective medicine is available for the prevention of influenza.

The US Centers for Disease Control and Prevention (CDC) recommends the administration of an influenza vaccine yearly for the prevention of influenza, but the efficacy varies yearly due to the emergence of new strains. According to the CDC, during the 2018–2019 influenza season, the vaccine was only 29% effective (Flannery 2019). Vaccines cannot offer complete protection because of high genetic diversity between and within influenza A and B types. Additionally, rapid antigenic drift and antigenic shift in the virus erodes vaccine durability (necessitating development of new vaccines annually), and slow vaccine manufacturing cycles make it difficult to keep pace with constantly mutating seasonal and pandemic viral strains.

The neuraminidase inhibitors (NAIs) oral oseltamivir and inhaled zanamivir are approved for prophylaxis and treatment of acute uncomplicated influenza. Use of NAI antiviral prophylaxis is recommended to control institutional outbreaks of influenza when used within 48 hours after exposure in individuals who are not vaccinated or who are unlikely to respond to influenza vaccines and are immunosuppressed or have co-morbidities that predispose them to severe influenza illness. However, when NAIs are used for prophylaxis, even when used promptly after a known exposure, the efficacy is only around 70–80% and prolonged use in immunocompromised individuals can lead to the emergence of NAI drug resistance (Okoli 2014).

Over the past 20 years there has been increasing concern that highly pathogenic avian strains such as H7N9 and H7N7 can be transmitted to humans causing high fatality rates in a manner similar to that of the H5N1 pandemic strain in 1997. Although the transmission of these avian strains to humans has been largely limited to individuals exposed to poultry, the possibility of the emergence of a highly pathogenic and human-adapted influenza variant is concerning (Paules 2017). Furthermore, recent modeling predicts that, in the event of a pandemic event along the lines of the 1918 Spanish flu, 33 million people would die in the first 6 months before a vaccine could be developed and many millions more would die during the time it would take for the global population to be immunized (Abbasi 2019).

Progress towards a medicinal agent that provides protection against a broad range of influenza strains with a longer duration of protection, otherwise known as a “universal vaccine”, has been disappointing. The monoclonal antibody (mAb) therapeutics developed to date have suffered from limited spectrum and commercial limitations due to high dosing requirements and/or the need for multiple antibody cocktails to achieve a desired spectrum and efficacy. Thus, a significant unmet need exists for long-acting universal protective agents.

4.1.2. CD388 – A Long-Acting Antiviral Fc-Conjugate

Cidara Therapeutics, Inc. (Cidara) is developing a novel therapeutic and prophylactic agent that has a potential to provide durable single-dose "universal" coverage per flu season. Cidara has replaced variable domains of a monoclonal antibody with multiple copies of a highly potent small molecule antiviral agent (the marketed NAI zanamivir) tailored to target a small, highly conserved essential influenza target. This molecule, CD388, is a first in class long-acting antiviral Fc-conjugate (AVC) combining a surface-acting antiviral agent with the crystallizable fragment (Fc) of a human immunoglobulin G1 (IgG1) antibody.

CD388 differs from traditional antibody-drug conjugate (ADC) molecules in the following aspects:

- In traditional antibody-drug conjugates the drug is attached to full length human IgG (Fc + antigen-binding fragment [Fab]); in contrast, zanamivir dimers of CD388 are conjugated to an Fc fragment of human IgG1 (and not full length IgG1).
- In traditional antibody-drug conjugates the drug is conjugated to the human IgG using a protease-cleavable linker to allow release of the drug inside target cells; the linker between zanamivir and the Fc in CD388 is not a substrate for proteases, and it exerts its antiviral activity in the extracellular space.
- Traditional antibody-drug conjugates are used to treat cancer by delivering cytotoxic payloads to target cells with rapid release; CD388 is designed to treat and prevent infectious disease using a long-acting stable conjugate of a non-cytotoxic small molecule to an Fc fragment of IgG1

In nonclinical in vitro and in vivo models, CD388 has demonstrated the potential for significantly higher antiviral activity and efficacy compared to the parent molecule, zanamivir, as well as other NAIs, including oseltamivir.

4.1.2.1. CD388 Nonclinical Studies

Several in vitro and in vivo nonclinical studies have been conducted to evaluate the safety and efficacy of CD388 and/or related Fc-conjugated prototype targeting molecules (TMs) to support dosing in humans. In vitro NAI and cell-based assays were conducted with CD388 to assess its spectrum and potency against Wild Type (WT) as well as drug-resistant influenza strains. In vitro studies to characterize the extent of neonatal crystallizable fragment receptor (FcRn) and Fc-γ receptor binding across different species were conducted. In vitro studies to characterize the potential for resistance development with CD388 have been undertaken. In vivo efficacy of CD388 was observed in treatment, and prophylaxis or preventative mouse lethal infection models.

In vitro stability of the TM compound alone was quantitatively tested at 37°C in phosphate-buffered saline, plasma, and liver microsomes. Stability of the intact Fc-conjugated molecule, CD388, was qualitatively observed in liver microsomes at 37°C. In vivo, the pharmacokinetics were investigated in animal species that were used to characterize the pharmacological and toxicological profile of CD388 and related molecules; namely in mouse, rat, and monkey. More importantly, following pharmacokinetic studies in the mouse, rat, and monkey, plasma concentrations were quantified by a neuraminidase (NA)-capture or Fc-capture with Fc detection

enzyme-linked immunosorbent assay (ELISA) methods, to confirm the stability of CD388 in vivo. NA-capture/Fc-detection measures the concentration of intact NA-linked-Fc species while Fc-capture/Fc-detection measures the total concentration of Fc-related species. Plasma concentrations measured by both methods were comparable, suggesting that intact CD388 remained stable in vivo as designed.

Single-dose, range-finding intramuscular (IM) and/or subcutaneous (SQ) toxicity and toxicokinetic studies, with endpoint evaluations occurring over the plasma exposure periods of 4 weeks in rats and 6 weeks in monkeys, have been conducted. The pivotal Good Laboratory Practice (GLP) toxicity studies include endpoints to assess safety pharmacology (i.e., cardiovascular, respiratory, and neurobehavioral effects) and toxicokinetics to determine safety margins. In addition, screening for anti-CD388 antibodies, cytokine analysis, and immunophenotyping have been performed. These pivotal GLP nonclinical studies supporting first-in-human (FIH) studies were designed in accordance with the relevant International Council for Harmonisation (ICH) guidance and US Food and Drug Administration (FDA) guidance on safety and toxicology studies for CD388's predecessor molecule (CD377).

Refer to the Investigator's Brochure for additional nonclinical information.

4.1.2.2. CD388 Clinical Studies

In an ongoing study (CD388.IM.SQ.1.01), the safety and tolerability of CD388 is being evaluated in Western healthy adult subjects, examining CD388 administered either intramuscularly or subcutaneously.

Regular assessment of blinded safety/tolerability data from 33 healthy subjects who received a dose of 50 mg, 150 mg, or 450 mg of subcutaneous CD388 or placebo has not identified any concerning safety observations to date.

All treatment-emergent adverse events (TEAEs) have been Grade 1 or Grade 2 (mild or moderate) in severity, with headache being the most frequently occurring (27.3% subjects), none of which occurred in the higher dose group (150 mg) as of the first Interim Analysis in the FIH study. Since then, preliminary safety data generated from the 450 mg dose group indicated that the safety and tolerability profile remained unchanged.

Of note, as of the first interim analysis in the FIH study, all TEAEs in the higher dose group (150 mg) have been Grade 1. No serious adverse events (SAEs) have occurred, and no drug-related TEAEs have resulted in clinically significant hematology or chemistry laboratory abnormalities. No safety issues associated with electrocardiograms (ECGs), vital signs, or physical examination findings (including local injection site reactions) have been identified. No safety findings have resulted in discontinuation or study drug or withdrawal from study. Preliminary safety data generated from the 450 mg dose group indicated that the safety and tolerability profile remained unchanged.

4.2. Summary of Benefits and Risks

A brief summary of clinical and nonclinical data is presented in Section 4.1.2.

The risks for the individual subject due to administration of CD388 Injection are considered low and are outweighed by the potential to develop a new treatment in an area of high unmet medical need. To further minimize any potential risk, all subjects will be closely screened for any

underlying conditions that may increase risk of study participation. During the conduct of the study, subjects are housed in a clinical research unit (CRU) for 14 days after CD388 Injection/placebo administration, under continuous medical supervision.

4.3. Justification of Dose

The dose(s) planned for this study are based on results obtained from the FIH clinical study, GLP 3-month exposure toxicology studies in rats and primates, and the FDA's guidance contained in "*Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*" (FDA 2005).

From the 3-month GLP toxicology studies in rats and monkeys, a no-observed-adverse-effect level (NOAEL) of 500 mg/kg has been established for both species. CD388 safety margins generated from these pivotal 3-month exposure studies in support of the dose are presented in Table 2. At the 50 mg human dose administered as a bolus SQ injection, the safety margin based on the 3-month NOAELs and using body surface area (BSA) is 97-fold in rats and 194-fold in monkeys. Safety margins based on human area under the plasma concentration-time curve (AUC) predictions at 50 mg relative to the rat and monkey 3-month plasma AUC exposures are 166-fold in rats and 581-fold in monkeys.

Table 2: Dose Levels and Safety Margins (Animal-to-Human Dose Ratios) for the Proposed CD388 50 mg Dose

3-Month Pivotal Toxicity Studies [c]	Animal Dose or Plasma Levels at NOAEL [a]				Safety Margins for 50 mg Human Dose Animal-to-Human Ratios [b]		
	mg/kg	mg/m^2 [d]	AUC (µg×h/mL) [e]	C_{max} (µg/mL)	Based on BSA	Based on Predicted Plasma AUC [f]	Based on Predicted Plasma C_{max} [f]
Rat	500	3000	641,000	1190	97-fold	166-fold	83-fold
Monkey	500	6000	2,240,000	3390	194-fold	581-fold	235-fold

Abbreviations: AUC = area under the plasma concentration-time curve; $AUC_{0–3month}$ = area under the plasma concentration-time curve from time 0 to 3 months; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 extrapolated to infinity; BSA = body surface area; C_{max} = maximum plasma concentration; FIH = first-in-human; IM = intramuscular; IV = intravenous; NOAEL = no-observed-adverse-effect level; PK = pharmacokinetic; SQ = subcutaneous.

a. NOAEL in rat and monkey 3-month studies.
b. Safety margins based on the proposed FIH dose of 50 mg or 0.833 mg/kg based on a 60 kg person, and 31 mg/m^2 based on a 1.62 m^2 person (FIH Guidance).
c. Repeat dose NOAEL from pivotal 3-month toxicity studies (NC CD388-004, NC-CD388-003).
d. The mg/m^2 dose was derived by multiplying mg/kg by 6 (rat) or 12 (cynomolgus monkey) (FIH Guidance).
e. Mean $AUC_{0–3month}$ values (males and females combined) calculated over 3 months: rat by summing AUC from 3 doses and monkey by summing AUC from 2 doses, to cover a 3-month exposure period.
f. Predicted human plasma PK for 50 mg starting dose (or 0.833 mg/kg based on a 60 kg person): $AUC_{0-\infty}$ = 3855 µg×h/mL. C_{max} = 14.4 µg/mL (calculated from 5 mg/kg IV human PK as reported/projected in NC-CD388-05). Note: These exposures were predicted for IV administration and would represent the highest values expected as bioavailability from IM or SQ administration is anticipated to be approximately 70% of IV based on animal PK studies, potentially lowering the exposures in human from IM or SQ dosing.

Safety results of the ongoing clinical trial CD388.IM.SQ.1.01 have indicated no significant safety findings following single SQ administration of 50, 150 mg, and 450 mg CD388.

In summary, excellent safety margins were achieved with CD388 in 3-month toxicity studies relative to the FIH human dose conservatively scaled to BSA and to the predicted FIH plasma exposure. Although no adverse findings were identified in nonclinical studies, transient minor changes in clinical pathology parameters were observed in the absence of other changes, including no changes in cytokines and microscopic findings, and no CD388-related effects on kidney or the reticuloendothelial system. The outcome of the CD388 nonclinical safety program supports the proposed clinical program and dose of 50 mg, 150 mg, and 450 mg administered as bolus SQ injections. Results from the FIH study to date have shown no significant safety findings after 50 mg, 150 mg, and 450 mg CD388 administrations.

4.4. Population to be Studied

Healthy adult Japanese subjects.

4.5. Rationale for Trial Endpoints

The measures for evaluation of the safety and tolerability profile of CD388 Injection are standard for most clinical studies and follow the recommendations in the ICH guidelines. The assessments for determining the plasma concentrations are appropriate to characterize the pharmacokinetic (PK) profile of CD388.

Exploratory biomarkers, anti-drug antibodies, and pharmacogenomic research are exploratory in nature and do not have pre-defined endpoints.

4.6. Statement of Compliance

This study will be conducted in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP), and applicable regulatory and IRB requirements.

5. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine the safety and tolerability profile of CD388 Injection when dosed by subcutaneous (SQ) administration as a single dose to healthy Japanese adult subjects.	• Incidence and severity of treatment-emergent adverse events (TEAEs), including but not limited to adverse events (AEs) and serious adverse events (SAEs) (including systemic reactogenicity/injection site reactions and hypersensitivity reactions), AEs leading to study drug discontinuation and/or study withdrawal, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory tests (including hematology, coagulation, serum chemistry, and urinalysis), after a single dose of CD388.
Secondary	
• To determine the plasma pharmacokinetic (PK) profile of CD388 Injection when dosed by SQ administration as a single dose to healthy Japanese adult subjects.	• Pharmacokinetic parameters following CD388 Injection administration: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{½}$), apparent clearance (CL/F), apparent volume of distribution (V_Z/F), area under the plasma concentration-time curve from time 0 to time of last quantifiable sample ($AUC_{0\text{-last}}$), area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$).
Exploratory	
• To evaluate the PK profile of CD388 in upper respiratory tract after SQ administration as a single dose to healthy Japanese adult subjects.	• Pharmacokinetic parameters following CD388 Injection administration: maximum nasopharyngeal (NP) concentration (C_{max}), time to maximum NP concentration (T_{max}), area under the NP concentration-time curve from time 0 to time of last quantifiable sample ($AUC_{0\text{-last}}$).
• To evaluate biomarkers that may be associated with safety, reactogenicity, and immunogenicity after CD388 Injection.	• Results of the analyses of exploratory biomarkers (including but not limited to cytokines, chemokines, acute phase reactants, etc.).
• To evaluate CD388 immunogenicity.	• Anti-drug antibody (ADA) titers in blood (plasma or serum).
• To explore the effect of CD388 Injection on the occurrence of influenza-like illness (during flu season).	• Occurrence of influenza-like illness reporting during the outpatient follow-up period.

6. STUDY DESIGN

6.1. Description of the Study

This is a Phase 1, single-center, prospective, randomized, double-blind study of ascending single doses of CD388 Injection administered SQ to healthy Japanese adult subjects. The goals are to assess safety, tolerability, and PK of CD388.

Subjects will be randomized to receive a single dose of CD388 or placebo administered via SQ injection (treatment assignment is blinded) according to the design in Table 3.

Table 3: Study Design

Number of Subjects (N = 27)		
Cohort: dose	**CD388 (n = 21)**	**Placebo (n = 6)**
Cohort 1: 50 mg	7	2
Cohort 2: 150 mg	7	2
Cohort 3: 450 mg	7	2

Note: A subject may not receive treatment in more than one cohort.

After 50% of Cohort 1 subjects have completed study drug administration and have undergone protocol-specified procedures and assessments for ≥10 days, the Principal Investigator (PI) and Sponsor will review blinded safety data: AEs (including systemic reactogenicity/injection site reactions, hypersensitivity reactions, and adverse events of special interest [AESIs]), vital signs, 12-lead ECGs, and clinical laboratory results (hematology, coagulation, serum chemistry, urinalysis) to determine the safety and tolerability of the study drug. The incidence and severity of AEs, and any adverse changes in vital signs, clinical laboratory findings, and ECGs will be considered when determining safety and tolerability of study drug. If the dose is determined to be safe and well tolerated ≥10 days after dosing, Cohort 2 will be enrolled. Enrollment of the remaining 50% of Cohort 1 will continue while the safety data of the first 50% of Cohort 1 is being reviewed. Similar processes will be followed for dose escalation from Cohort 2 to Cohort 3.

The Schedule of Events is presented in Table 1. All subjects will be admitted to the clinical research unit (CRU) for observation and safety assessments from Day -1 (check-in) to Day 14. Subjects will be monitored for AEs (including systemic reactogenicity/injection site reactions, hypersensitivity reactions, and AESIs) and SAEs throughout the study until the final study visit after dosing. Safety will also be assessed by physical examinations, ECGs, vital signs measurements, and laboratory evaluations (hematology, coagulation, serum chemistry, urinalysis) at various time points during and after the CRU stay. Concomitant medication use will be recorded throughout the study.

Blood samples for PK and ADA assessments will be collected throughout the study. To maintain the blind, samples will be collected from all subjects; however, only samples from the CD388 Injection group will be analyzed (using validated assays) by an unblinded central bioanalytical laboratory. Additional blood samples will be collected for pharmacogenomics and exploratory biomarker evaluation.

Respiratory tract infection (RTI) surveillance will be conducted during the outpatient phase of the study from CRU discharge through the Day 120/165 outpatient visit or a lab-confirmed influenza infection, whichever occurs first. Subjects will be provided nasal/throat swab kits (for detection of influenza infection or other respiratory pathogen by a multiplexed polymerase chain reaction [PCR] test) and symptom diary cards.

If 3 or more RTI symptoms listed in the table below occur (at least one must be a respiratory symptom), subjects will contact study staff, then collect nasal/throat swab samples (the swabs should take place as soon as possible after the start of symptoms, ideally within 48 hours, but no later than 5 days). Subjects will complete symptom diary cards every 7 days to capture the worst grade of symptoms that occurred during the previous week. The Investigator/study staff will arrange for prompt shipment of the nasal/throat samples to the testing laboratory. Note: If the reported symptoms are already of a level of severity that urgent care is indicated, the subject should be directed to the appropriate facility to receive this care (e.g., emergency room). Otherwise, symptoms should be treated according to standard of care.

If an influenza infection is confirmed by the testing laboratory before the Day 120/165 outpatient visit, the event should be documented until all symptoms have resolved, including completion of the symptom diary card every 7 days. Thereafter, no further RTI surveillance will be carried out on the subject.

If the nasal/throat swab samples are not confirmed to be influenza by the testing laboratory, diary card completion will continue through the Day 120/165 outpatient visit.

Respiratory Tract Infection (RTI) Symptoms	
• Runny nose (rhinorrhea)	• Shortness of breath (dyspnea)
• Stuffy nose (nasal congestion)	• Wheeze
• Sore throat	• Chilliness/feverishness or temperature ≥100°F
• Earache	• Headache
• Cough	• Body ache
• Productive phlegm/sputum	

As part of the surveillance, subjects will be questioned during all outpatient site visits for RTI symptoms. If the interval to the next outpatient site visit exceeds 15 days, subjects will be contacted by the Investigator/study staff every 2 weeks to query for RTI symptoms. Subjects should be reminded to contact the Investigator/study staff if RTI symptoms occur, and to collect the nasal/throat swab samples and complete the symptom diary cards every 7 days.

6.2. Criteria for Evaluation

6.2.1. Safety and Tolerability of Study Drug

Safety and tolerability will be assessed by monitoring AEs (including systemic reactogenicity/ injection site reactions, hypersensitivity reactions, and AESIs), vital signs, 12-lead ECGs, clinical laboratory results (hematology, coagulation, serum chemistry, urinalysis), and concomitant medication usage throughout the study.

See Section 6.1 for details regarding cohort/dose level enrollment timing and assessment of safety and tolerability for dose escalation decision.

If a dose level is considered not safe or well tolerated, the study drug assignment for the subject(s) with the safety issue may be unblinded. The Sponsor may also independently decide to unblind the entire cohort for safety concerns or terminate enrollment for any reason.

If any subject develops a Grade ≥2 AE or an SAE of any grade that is deemed related to the study drug, the mechanism of the AE may be assessed (i.e., cytokine level, complement activation, immunoglobulin G [IgG] subtypes, immunoglobulin E [IgE], T-cell/B-cell/monocyte and basophil activation as assessed by flow cytometry, ADA development, and immune complex formation) at Sponsor and Investigator discretion, and the study dose may be modified for the remainder of the study.

6.2.2. Pharmacokinetics/Anti-drug Antibodies

Pharmacokinetics will be determined by analyzing plasma samples for concentration of CD388 obtained from subjects who receive CD388 Injection in each cohort at various time points after administration of study drug. Anti-drug antibodies will also be measured at selected time points by a validated ELISA method.

6.2.3. Pharmacogenomics

A mandatory pharmacogenomic (DNA) blood sample will be collected once, preferably on Day 1 (collection at another time point is permitted if necessary) to allow for genetic research to help understand the characteristics of CD388. Genetic analysis will be conducted if it is hypothesized that doing so may aid in exploring genetic markers which could explain differences in safety, immunogenicity, or clinical response among subjects. Host DNA assessment will be limited to research related to CD388, including the development of tests/assays related to CD388 and flu-like disease.

Analyses of host DNA may be conducted at the Sponsor's discretion and reported separately from the study report.

6.2.4. Exploratory Biomarkers

Blood samples will be collected to allow for the exploration of biomarkers on the assumption that these markers could play a role in the response (safety, reactogenicity, immunogenicity) to CD388.

These samples and remaining material from other samples may be used for further assay optimization/qualification, biomarkers, or further exploratory analyses. Samples will only be used for research related to influenza virus infection, flu-like disease, and safety, reactogenicity, and immunogenicity of CD388, including the development of tests/assays related to CD388 and influenza.

Analyses of biomarkers may be conducted at the Sponsor's discretion and reported separately from the study report.

6.3. Number of Subjects

A total of 27 healthy volunteers will be enrolled in this study in 3 cohorts: 9 of the 27 subjects will be enrolled in the first cohort and randomized in a 7:2 ratio to receive either 50 mg CD388 SQ injection or matching placebo injection; the remaining subjects will be enrolled in the second

and third cohorts (9 subjects each) and randomized in a 7:2 ratio to receive either 150 mg (Cohort 2) or 450 mg (Cohort 3) CD388 SQ injection or matching placebo injection.

6.4. Measures Taken to Minimize Bias

Study drug assignment (CD388 Injection or placebo) will be blinded to all blinded clinical site and Sponsor study team until at least after the final subject in a cohort has completed the Day 90 visit. Unblinded personnel include the site pharmacist (or pharmacist designee) preparing the injections, the unblinded pharmacy monitor (to ensure study drug accountability and assignment throughout the trial), and the Sponsor's unblinded team.

6.5. Expected Duration of Subject Participation

A single dose of study drug will be administered SQ on Day 1. Study participation will require up to 28 days for screening procedures, and approximately 120/165 days for dosing and follow-up (check-in to the CRU on Day -1; CRU inpatient stay for study drug administration, observation, and assessments and procedures for 15 days [Days -1 to Day 14]; and 5 CRU outpatient visits for additional assessments and procedures).

6.6. Method of Treatment Assignment and Blinding

After informed consent has been obtained, subjects will be screened for study eligibility before randomization.

Within each dose level (Cohorts 1, 2, and 3), subjects will be randomized to receive a single dose of CD388 Injection or saline placebo (treatment assignment is blinded). The study site's pharmacist (or pharmacist designee) will obtain a computer-generated study drug assignment. A subject is considered randomized when a randomization transaction is appropriately recorded.

Unless a formal interim analysis is conducted after all subjects have completed the Day 90 visit, all blinded study personnel (including the Sponsor, Investigator, and site personnel directly involved in study conduct) and subjects will remain blinded to study drug assignment until the study is completed and the final database is locked with the exception of the unblinded pharmacy personnel, pharmacy monitor, and unblinded Sponsor personnel (such as Data Review Committee, clinical supply manager, PK lead, and quality manager) who may be unblinded to study medication at any time during study conduct. The pharmacy monitor will monitor study drug preparation and accountability during the study and cases in which unblinding is required due to a safety or tolerability issue. To maintain study blinding, study drug preparation will be performed by an unblinded site pharmacist (or qualified unblinded personnel at the study site not involved with study procedures or evaluations). Any unblinding related to an interim analysis will be documented in the blinding plan.

Instructions for study drug preparation and dosing are outlined in the Pharmacy Manual provided separately to the site. In the event of a medical emergency requiring the Investigator to know the identity of the study drug, the Investigator will follow the procedures outlined in Section 8.4.

6.7. Data Review Committee

A Sponsor Data Review Committee, consisting of representatives of the Sponsor not involved in day-to-day management of the study, may be established to review unblinded data to allow

strategic development decisions within and across development programs. The procedures of the Data Review Committee will be documented in a charter.

7. SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Subjects must meet ALL the following inclusion criteria:

1. Must be of Japanese descent with Japanese parents and grandparents, as determined by subject's verbal report.
2. Willing and able to provide written informed consent.
3. Males and females 18 to 65 years of age, inclusive.
4. A female subject must meet one of the following criteria:
    a. If of childbearing potential – agrees to use a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) for at least 30 days prior to screening and agrees to remain on a highly effective method until 7 months after last dose of study medication. Examples of highly-effective methods of contraception are located in Appendix 1.
    b. If a female of non-childbearing potential – should be surgically sterile (i.e., has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation/occlusion without reversal surgery) or in a menopausal state (at least 1 year without menses), as confirmed by follicle-stimulating hormone (FSH) levels (≥40 mIU/mL).
5. A woman of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin) at screening and a negative urine pregnancy test on Day -1 before the first dose of study drug.
6. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of at least 7 months after study drug administration.
7. A male subject that engages in sexual activity that has the risk of pregnancy must agree to use a double barrier method (e.g., condom and spermicide) and agree not to donate sperm during the study and for at least 7 months after the last dose of the study medication.
8. Good health and without signs or symptoms of current illness.
9. Normal clinical examination, including:
    a. No physical examination findings that an Investigator determines would interfere with interpretation of study results.
    b. Screening ECG without clinically significant abnormalities (see Appendix 2).
    c. Creatinine clearance (CrCL) ≥80 mL/min as calculated using the Cockcroft-Gault equation:

$$CrCL = \frac{(140 - age) \times (weight\ in\ kg)}{72 \times (serum\ creatinine\ in\ mg/dL)} \times (0.85\ if\ female)$$

d. Negative urine screen for drugs of abuse and alcohol at screening and Day -1.

10. Body weight ≥50 kg and body mass index between 18.0 and 30.0 kg/m^2, inclusive, using the following equation:

$$BMI = \frac{(weight\ in\ kg)}{(height\ in\ meters)^2}$$

11. Willing to refrain from strenuous physical activity that could cause muscle aches or injury, including contact sports, at any time from screening through 30 days after any dose of study drug.
12. Subject has adequate venous access for blood collection.

7.2. Subject Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria:

1. History of any hypersensitivity or allergic reaction to zanamivir or other neuraminidase inhibitors (i.e., laninamivir, oseltamivir, peramivir), or to excipients of the CD388 Injection drug formulation; or history of drug-induced exfoliative skin disorders (e.g., Stevens-Johnson syndrome [SJS], erythema multiforme, or toxic epidermal necrolysis [TEN]).
2. History of any of the following:
   a. Allergies, anaphylaxis, skin rashes (foods such as milk, eggs, medications, vaccines, polyethylene glycol [PEG], etc.).
   b. Chronic immune-mediated disease, positive first-degree family history of autoimmune diseases.
   c. Atopic dermatitis or psoriasis.
   d. Bleeding disorder.
   e. Psychiatric condition, seizures, hallucinations, anxiety, depression, or treatment for mental conditions.
   f. Migraines.
   g. Syncope, or vasovagal syndrome with injections or blood draws.
   h. Cardiac arrythmia considered clinically significant by the Investigator.
3. Subjects with one or more of the following laboratory abnormalities at screening as defined by the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events v2.1 (DAIDS 2017):
   a. Serum creatinine, Grade ≥1 (≥1.1 × upper limit of normal [ULN]).
   b. Pancreatic amylase or lipase, Grade ≥2 (≥1.5 × ULN).
   c. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT), Grade ≥1 (≥1.25 × ULN).
   d. Total bilirubin, Grade ≥1 (≥1.1 × ULN).

e. Any other toxicity Grade ≥2, except for Grade 2 elevations of triglycerides, low density lipoprotein cholesterol, and/or total cholesterol.

f. Any other laboratory abnormality considered to be clinically significant by the Investigator.

Note: Retesting of abnormal laboratory values that may lead to exclusion will be allowed once without prior asking approval from the Sponsor. Retesting will take place during a scheduled or unscheduled visit during screening. Subjects with a normal value at retest may be included.

4. Alcohol or drug addiction in the past 2 years.
5. Experiencing symptoms of acute illness or chronic disease within 14 days prior to clinical research unit (CRU) check-in.
6. At screening, a positive result for hepatitis B virus surface antigen, hepatitis C virus antibody, or human immunodeficiency virus (HIV) antibody.
7. A positive result at CRU check-in for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by polymerase chain reaction (PCR).
8. Unwilling to comply with local health policy effective at the time regarding coronavirus disease 2019 (COVID-19). Full COVID-19 vaccination prior to participation is strongly recommended.
9. Women who are pregnant or nursing.
10. Received any over-the-counter (OTC) medications or nutritional supplements within 7 days, or any prescription medications within 14 days or <5 half-lives prior to dosing, whichever is longest (except for hormonal contraceptives, acetaminophen, or ibuprofen).
11. Current nicotine user or has quit habitual nicotine use in the 30 days prior to screening.
12. Received any vaccines or immunoglobulins within 28 days prior to dosing (90 days in case of intravenous immunoglobulin [IVIg] or biologics, or 14 days for COVID-19 vaccine).
13. Donated blood (within 56 days of screening) or plasma (within 7 days of screening) or experienced significant blood loss or significant blood draw (blood donation or blood loss of ≥500 mL) when participating in non-interventional clinical trials within 30 days prior to dosing.
14. Received a blood transfusion within 28 days prior to dosing.
15. Received any biologics within 90 days prior to dosing; or previous participation in another study (including investigational device studies) within 30 days of dosing or 5 half-lives of the study drug, whichever is longer, prior to screening (prior participation at any time in non-invasive methodology trials in which no drugs were given is acceptable).
16. Previous treatment with CD388.
17. Preplanned surgery at any time during the study.

18. The Principal Investigator (PI) considers that the volunteer should not participate in the study.

7.3. Requalification for Entry

Subjects not fulfilling the entry criteria and not randomized may be rescreened for participation with the approval of the Sponsor Medical Monitor. A subject who rescreens will receive a new screening number.

7.4. Subject Withdrawal Criteria

7.4.1. Withdrawal from Study Protocol

Subjects may withdraw consent to participate in this study at any time without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who wish to withdraw completely from this clinical study should be encouraged to complete the Day 120/165 assessments. Every reasonable effort should be made to determine the reason a subject withdraws prematurely, and this information should be recorded on the appropriate page(s) of the electronic case report form (eCRF).

Subjects may be withdrawn from the study for any of the following reasons:

- Subject is unable or unwilling to continue
- Subject elects to withdraw informed consent
- Adverse event (whether or not related to study drug) that precludes further participation in the study in the judgment of an Investigator and/or Sponsor
- Protocol non-compliance
- Subject lost to follow-up, or follow-up is not possible
- The Investigator considers that it is in the subject's best interest not to continue participation in the study

If a subject is removed from the study for any reason, the subject will be followed for resolution of any ongoing AE(s).

7.5. Replacement of Subjects

Subjects who are withdrawn for reasons other than AEs may be replaced at the discretion of the Sponsor into the same cohort and blinded treatment assignment as the replaced subject.

7.6. Temporary Study Halt for Safety Review

The study will be temporarily halted, pending review of available data, if any of the following occur:

- If ≥2 subjects experience the same Grade 3 AE event or laboratory abnormality within 28 days after study drug administration, considered attributable to CD388 or cannot be attributed to another cause

- If ≥1 subject experiences a Grade 4 AE or laboratory abnormality within 28 days after study drug administration, considered attributable to CD388 or cannot be attributed to another cause
- If ≥1 subject experiences an SAE irrespective of toxicity grade within 28 days after study drug administration, considered attributable to CD388 or cannot be attributed to another cause

If it is considered appropriate to restart the study following an internal safety review, an amendment, if required, will be submitted to the FDA and IRB. The study will not restart until the amendment has been approved by the FDA and IRB.

7.7. Study Termination by Sponsor and Termination Criteria

The Sponsor reserves the right to terminate an investigational site or this clinical study at any time. Reasons for termination may include, but are not limited to, the following:

- The incidence or severity of AEs indicate a potential health hazard to subjects.
- Serious or persistent noncompliance by the Investigator with the protocol, clinical research agreement, or applicable regulatory guidelines in conducting the study.
- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) decision to terminate or suspend approval for the investigation or the Investigator.
- Investigator request to withdraw from participation.
- Subject enrollment is unsatisfactory.

8. STUDY DRUG

8.1. CD388 Injection

CD388 Injection is a clear to lightly opalescent liquid essentially free of particulate matter containing the active pharmaceutical ingredient, CD388. CD388 Injection is supplied as a frozen sterile solution in single-use vials. Refer to the Pharmacy Manual for details.

CD388 Injection is administered by SQ injection at the doses described in Table 3. Dose levels to be assessed will follow an ascending single-dose regimen with the starting dose based on findings from 3-month rat and monkey toxicology studies.

8.1.1. Directions for Use

CD388 Injection should be thawed at room temperature over 30 minutes (not to exceed 24 hours) prior to drawing the dose from the vial into the syringe.

After CD388 Injection is drawn from the vial into the syringe, it must be administered within 4 hours.

8.1.2. Drug Storage

Vials of CD388 Injection are stored frozen at -20°C.

8.1.3. Dose Adjustment

Dosage adjustments of CD388 Injection in individual subjects are not allowed in this study.

8.2. Placebo Injection

Normal saline will be administered SQ as the placebo control.

8.3. Compliance

Treatment compliance for CD388 Injection/placebo will be documented in the eCRF by recording the date, administration time, and the volume of the dose of study drug administered.

8.4. Breaking the Blind

The study is a double-blind design. The Sponsor, Investigator, study site personnel, and subjects will not make any effort to determine which blinded study drug (CD388 Injection or placebo) is administered. Unblinded pharmacy personnel will be responsible for preparing syringes such that the double-blind is maintained.

Only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific subject, may the Investigator unblind a subject's study drug assignment.

As soon as possible and without revealing the subject's study drug assignment (unless important to the safety of subjects remaining in the study), the Investigator must notify the Sponsor if the blind is broken for any reason. The Investigator will record in source documentation the date and reason for revealing the blinded study drug assignment for that subject.

As PK samples from subjects assigned to placebo treatment will not be analyzed for determination of CD388 concentrations, the bioanalytical laboratory will receive the randomization list to allow for correct selection of the samples. Unblinding of the randomized treatment assignment will be performed at the bioanalytical laboratory. Specific procedures will be in place to ensure that randomized treatment assignment will not be revealed to anyone involved in the execution of the study.

8.5. Previous and Concomitant Medications and Substances

All medications administered within 28 days prior to study drug administration and throughout the study will be documented and recorded in the eCRF.

Subjects must refrain from OTC, herbal medications, and nutritional supplements within 7 days and prescription medications within 14 days or <5 half-lives before first study drug administration, and until after the final study visit (except for hormonal contraceptives, acetaminophen, or ibuprofen). The Investigator should consult the Sponsor's Medical Monitor for guidance regarding other medication or vaccine usage during the study.

8.6. Accountability Procedures

The pharmacy or study personnel are responsible for ensuring that a current record of CD388 Injection inventory and accountability are maintained.

A Pharmacy Monitor will be responsible for checking drug accountability at the site. Inventory records must be readily available for inspection by regulatory authorities at any time. Each shipment of study drug will require acknowledgment of receipt. Upon receipt of study drug, the pharmacy or study personnel will visually inspect the shipment and verify the number and condition of vials received. Refer to the Pharmacy Manual for additional information.

8.7. Study Drug Handling and Disposal

Unless expressly disallowed by institution rules or local regulations, used and unused vials of CD388 Injection will be retained at the study site until study drug accountability has been performed by the Pharmacy Monitor. Upon completion of the study, termination of the study, or upon written authorization from the Sponsor, all retained unused and partially used study drug will be centrally destroyed or destroyed at the site upon written authorization from Sponsor, unless expressly disallowed by local regulations. Adequate documentation to support destruction is required prior to destruction of the vials, and a certificate of destruction or written documentation that specifies the date, quantity, lot numbers, and method of destruction that is traceable to the study drug must be provided to the Sponsor. All records of disposal will be maintained by the Sponsor.

9. STUDY PROCEDURES

The Schedule of Events (Table 1) summarizes the frequency and timing of all applicable study assessments, including allowable windows for study visits and assessments/procedures. Written informed consent must be obtained before any study-related procedures are performed.

All procedures should be completed as close to the prescribed/scheduled time as possible. Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

When multiple assessments are scheduled at the same time point, perform the assessments in the following order: 12-lead ECG, vital signs, and blood sample collection.

9.1. Medical History

A complete medical history will be recorded, including demographic information (age, gender, race, and ethnicity).

9.2. Physical Examinations

A complete physical examination is required at screening. Targeted (i.e., symptom directed) physical examinations may be performed at all other indicated visits, and as clinically indicated.

9.3. Vital Signs

Vital signs include blood pressure (systolic and diastolic), heart rate, respiration rate, and oral temperature, and will be measured with the subject in a seated position for at least 3 minutes prior to measurement. Height and weight are to be measured and body mass index (BMI) calculated when indicated.

9.4. Electrocardiograms

Subjects should be resting (at least 5 minutes) and semi-recumbent for safety triplicate 12-lead ECGs. Data collection includes abnormal findings; if abnormal finding(s) are assessed as clinically significant, the finding(s) should be reported as AE(s). The Investigator is responsible for interpreting and measuring ECG data.

The screening ECG may be repeated once to confirm eligibility.

9.5. Laboratory Evaluations

Blood and urine for laboratory evaluations will be collected and analyzed at a laboratory in accordance with quality laboratory standards. Hematology, serum chemistry, coagulation, urinalysis, and other parameters to be tested are listed in Table 4.

Table 4: Clinical Laboratory Tests

Test Category	Specific Laboratory Tests	
Hematology: [a]	Hemoglobin	Neutrophils (absolute)
	Hematocrit	Monocytes (absolute)
	Erythrocyte (red blood count [RBC]) count	Eosinophils (absolute)
	Quantitative platelet count	Lymphocytes (absolute)
	Total leukocyte (white blood cell [WBC]) count	Basophils (absolute)
	Mean corpuscular hemoglobin (MCH)	Mean corpuscular volume (MCV)
Serum Chemistry: [a]	Aspartate aminotransferase (AST)	Calcium
	Alanine aminotransferase (ALT)	CO_2 or bicarbonate
	Alkaline phosphatase (ALP)	Blood urea nitrogen (BUN) or urea
	Albumin	Creatinine
	Total bilirubin (if total bilirubin is ≥2 × ULN with no evidence of Gilbert's syndrome, then fractionate into direct and indirect bilirubin)	Glucose
	Sodium	Chloride
	Potassium	Lipase
	Total protein	Lactate dehydrogenase (LDH)
	Phosphorus	Amylase
	Creatinine Clearance (Cockcroft-Gault)	
Lipids: [b]	Triglycerides	Low Density Lipoproteins (LDL)
	Cholesterol, Total	
Coagulation: [b]	Activated partial thromboplastin time (aPTT)	International normalized ratio for prothrombin time (INR/PT)
Complement Activation: [b]	Complement C3, C4, CH50	
Urinalysis: [a]	pH	Occult blood
	Protein	Specific gravity
	Glucose	Ketones
	Appearance	Color
	Bilirubin	Leukocyte esterase
	Nitrite	Microscopic reflex if protein, nitrite, blood or leukocyte esterase are positive (WBC, RBC, epithelial cells, bacteria, casts, other findings)
Serology:	Hepatitis B surface antigen (HBsAg) [c]	Human immunodeficiency virus (HIV) antibody [c]
	Hepatitis C antibody [c]	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) [d]

Pregnancy: [e]	Serum beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential (screening and Day 120/165 only), urine or serum test at all other specified visits	Follicle-stimulating hormone (FSH), if applicable to confirm postmenopausal status, is only required once
Other: [f]	Drug (opioids, benzodiazepines, barbiturates, cocaine metabolites, cannabinoids, methamphetamines, phencyclidine, amphetamine, cotinine) and alcohol screen	

a. At each visit indicated in the Schedule of Events (Table 1).
b. Performed at screening, and as clinically indicated (e.g., if the Investigator has concerns regarding an SAE, anti-drug antibody reaction in a subject with hypersensitivity reaction, fever, serious rash, joint/bone pain, cough, proteinuria, or clinically meaningful changes in the white cell differential or liver function tests).
c. At screening only.
d. If a subject develops signs and symptoms of an acute respiratory tract infection at any time during the study, COVID-19, influenza, and/or respiratory syncytial virus (RSV), nasopharyngeal rapid antigen test plus PCR will be performed.
e. As indicated.
f. At screening and Day -1, and during the outpatient visits if vital signs are abnormal.

9.6. Randomization

For randomization procedures, see Section 6.6.

9.7. Pharmacokinetics, Pharmacogenomics, Exploratory Biomarkers, and Anti-drug Antibodies

Blood and NP swab samples for pharmacokinetic analysis, pharmacogenomics, exploratory biomarkers, and anti-drug antibodies will be collected as indicated in the Schedule of Events (Table 1). Refer to the laboratory manual for instructions on collection of these samples for analysis.

Refer to the laboratory manual for instructions on collection of samples from nasopharyngeal swab for exploratory CD388 assays.

9.8. Reactogenicity/Injection Site Inspection

At indicated visits, inspection of administration site and surrounding area will be performed twice daily, with any abnormal findings reported as AEs. Reactions will be rated according to Table 5.

Table 5: Injection Site Evaluation

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness [a]	2.5–5 cm	5.1–10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling [b]	2.5–5 cm and does not interfere with activity	5.1–10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

a. In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

b. Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Source: (FDA 2007).

9.9. Adverse Events

Information on AEs (event term, start and stop dates, severity, relationship to blinded study drug) will be collected from the time of signing the informed consent form (ICF) until the final study visit after the dose of study drug. See Section 11 for additional information.

9.10. Prior and Concomitant Medications and Concomitant Procedures

Prior and concomitant medication usage will be recorded from 28 days prior to CD388 Injection/placebo administration until the final study visit. See Section 8.5 for permitted concomitant medications.

Concomitant procedures to treat an AE will be recorded from the time of CD388 Injection/ placebo administration until the final study visit.

10. ASSESSMENT OF EFFICACY

Not applicable; this study has no efficacy endpoints.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

Safety and tolerability will be assessed by monitoring AEs (including systemic reactogenicity/injection site reactions, hypersensitivity reactions, and AESIs), vital signs, 12-lead ECGs, clinical laboratory results (hematology, coagulation, serum chemistry, urinalysis), and concomitant medication usage throughout the study.

11.2. Adverse Events

Adverse events will be collected for all subjects from the time of signing the ICF through the final study visit. The Investigator will assess all AEs and SAEs and will record the following information on the appropriate eCRF page:

- Date of onset
- Resolution status, and date of resolution or stabilization if achieved
- Seriousness
- Severity
- Causal relationship to study drug
- Action taken with study medication

Medically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory. The Investigator should employ best medical judgment in determining how to manage AEs and SAEs. Any questions regarding AE or SAE management should be directed to the Medical Monitor.

The Sponsor is responsible for:

- Confirming the seriousness assessment of all reported AEs and SAEs
- Confirming the causal relationship between reported AEs/SAEs and the investigational product
- Assessment of SAEs for expectedness

The Sponsor will continuously assess the safety of the investigational product throughout the study.

11.3. Adverse Event Reporting

11.3.1. Notification of Serious Adverse Events

The Sponsor has requirements for expedited reporting of SAEs meeting specific criteria to worldwide regulatory authorities in accordance with ICH guidelines and local regulatory requirements. Therefore, the Investigator must notify the Sponsor immediately regarding any SAE that occurs after informed consent via transmission of a Serious Adverse Event Report (SAER) by the study site to the safety vendor by email within 24 hours of awareness that an SAE

has occurred, with a copy to the Medical Monitor. Contact details will be provided to the site(s). An optional initial report can be made via telephone, but a completed SAER must still be emailed within 24 hours of the site's knowledge of the event.

The Investigational site will be provided with SAER forms wherein the following information is requested:

- Subject identification, Investigator name, and site number
- SAE information: event term, onset date, severity, and causal relationship
- The outcomes attributable to the event (e.g., death, a life-threatening AE, inpatient hospitalization, prolongation of existing hospitalization, a persistent or significant disability or incapacity, or other important medical event[s]; refer to Section 11.4.4)
- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history
- The date of study drug administration (NOTE: as this is a double-blind study, SAERs should not indicate specific study drug assignments)

Supplemental information may be requested, including the following: hospital records, laboratory results, radiology reports, progress notes, admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

Relevant eCRF pages can be appended to communicate information relevant to the SAE, including study drug administration details, medical history, concomitant medications, relevant laboratory test results, and subject outcome information. The SAER should be emailed within 24 hours with as much of the above information as available at the time. The following minimum information is required for reporting an SAE: subject identification, Investigator contact information, an AE with a serious outcome, and the Investigator's assessment of causal relationship to study drug. Serious adverse events are to be reported immediately and under no circumstance should this reporting time exceed 24 hours following knowledge of the SAE. Supplemental information may be transmitted using a follow-up report and should not delay the initial report. The Sponsor may contact the investigational site to solicit additional information or follow up on the event.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the subject's eCRF.

If the Investigator becomes aware of any SAEs that occur after the study period that are believed to be causally related to use of the investigational product, they should notify the Sponsor immediately.

The Sponsor will report all suspected unexpected serious adverse reactions (SUSARs) within the required regulatory timeframes to all applicable regulatory authorities and to Investigators as required.

All SAEs that do not meet expedited reporting requirements will be summarized in the Development Safety Update Report (DSUR) and reported annually by the Sponsor as required.

11.3.2. Notification of Emerging Safety Issues

Additionally, the Investigator should alert the Sponsor immediately (under no circumstance should this reporting time exceed 24 hours) by contacting the Medical Monitor of any new findings that necessitate the implementation of urgent safety measures to protect subjects against any immediate hazard. If time permits, the Investigator should contact the Sponsor to discuss the hazard and any actions taken or to be taken prior to implementation.

The Sponsor is responsible for informing other investigators who may need to implement the same procedures and for alerting the Competent Authorities and Ethics Committees of the new findings and measures taken in accordance with local regulations within the required timeframes.

11.4. Definitions

11.4.1. Adverse Event

An AE means any untoward medical occurrence associated with the use of a drug or study procedure in humans, whether or not considered drug-related. An AE can be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Laboratory abnormalities should not be recorded as AEs or SAEs unless they are associated with clinical signs or symptoms, or require medical intervention. However, each laboratory abnormality (e.g., clinically significant changes detected on hematology, coagulation, chemistry, urinalysis) independent from any underlying medical condition that requires medical or surgical intervention, or that leads to interruption of study drug or discontinuation, must be recorded as an AE, or SAE if applicable. If the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than as the individual laboratory abnormality. In addition, laboratory abnormalities or other abnormal test assessments (e.g., ECGs) that are associated with signs or symptoms must be recorded as AEs or SAEs if they meet the definition of an AE or SAE as described in this section and in Section 11.4.4, respectively.

11.4.2. Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. "Suspected adverse reaction" implies a lesser degree of certainty about causality than "adverse reaction", which means any AE caused by a drug.

11.4.3. Life-Threatening AE or Life-Threatening Suspected Adverse Reaction

An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

11.4.4. Serious Adverse Event or Serious Suspected Adverse Reaction

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect in the offspring of a subject who received study drug
- Is a suspected transmission of any infectious agent via a medicinal product
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

11.4.5. Unexpected AE or Unexpected Suspected Adverse Reaction

An AE or suspected adverse reaction is considered "unexpected":

- If it is not listed in the Investigator's Brochure or is not listed at the nature, severity, frequency, or outcome that has been observed

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

"Unexpected", as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

11.4.6. Adverse Events of Special Interest

Adverse events of special interest (AESIs) include anaphylaxis (refer to Appendix 3 for diagnostic criteria and management).

11.4.7. Emerging Safety Issue

Any new safety information that may lead to a reassessment of the risk/benefit balance of the investigational product and/or impact subjects' health. Examples include:

- Any new safety issue relating to the conduct of the clinical trial that may impact the safety of the trial subjects such as significant safety results from a recently completed non-clinical study or early termination or temporary suspension of a trial for safety reasons that is conducted on the same investigational product

- Recommendations from a Data Review Committee that may affect the safety of trial subjects

11.4.8. Urgent Safety Measure

An urgent safety measure (USM) is a procedure not defined by the protocol that can be put in place immediately, without prior authorization from Ethics Committees or Regulatory Authorities, to protect study subjects from any immediate hazard to their health and safety.

11.5. Adverse Event Classification

11.5.1. Relationship to Study Drug

The Investigator's assessment of causality must be provided for all AEs (serious and nonserious; Table 6). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is thought to be unrelated to study drug administration, an alternative explanation should be provided.

Table 6: Table Guidelines for Assessing Relationship of Event to Study Drug

Unrelated	There is little or no chance that the study drug caused the adverse event (AE); other conditions, including concurrent illnesses, progression or expression of the disease state, or a reaction to a concomitant medication best explain the event.
Related	The association of the AE with the study drug is unknown; however, the AE is not clearly due to another condition, or a reasonable temporal association exists between the AE and study drug administration and, based on the Investigator's clinical experience, the association of the AE with the study drug seems likely.

11.5.2. Severity

For injection site reactions, the Investigator will use the grading scale in Table 5. To describe the intensity of all other AEs following general categorical descriptors outlined in the DAIDS table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS 2017), the grading scale in Table 7 will be used.

Table 7: Guidelines for Severity Assessments

Grade 1 Mild	Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated
Grade 2 Moderate	Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated
Grade 3 Severe	Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated
Grade 4 Potentially Life Threatening	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
Grade 5 Death	Fatal

Refer to the DAIDS table for Grading the Severity of Adult and Pediatric Adverse Events for details regarding event grading.

11.5.3. Serious Adverse Event

Any adverse experience occurring at any dose of study medication that occurs from the time of informed consent through the final study visit, are considered serious if they result in any of the outcomes listed in Section 11.4.4.

Hospitalization for a planned or elective procedure or surgery for a pre-existing condition that has not worsened is not considered an SAE.

11.6. Adverse Event Follow Up

All unresolved SAEs and study drug-related AEs will be followed by the study staff until resolution or deemed stable, regardless of severity.

11.7. Adverse Event Management

The Investigator should employ best medical judgement in determining how to manage AEs. Any questions regarding AE management should be directed to the Medical Monitor.

11.8. Risks for Women of Childbearing Potential or During Pregnancy

The risks of CD388 Injection in pregnant or lactating/nursing women are unknown. Pregnant or nursing female subjects are excluded from this study.

Subjects must be instructed to inform the Investigator immediately if they or their partner becomes pregnant during the study. In the case of a partner pregnancy, partner informed consent must be obtained prior to collecting information related to the pregnancy and to allow the Investigator to follow them for the outcome of the pregnancy. In the event of a confirmed pregnancy, the following actions should be taken:

- The pregnancy should be reported to the Sponsor within 24 hours of the subject notifying the Investigator using the applicable Pregnancy Report Form.
- The Investigator should counsel female subjects regarding the possible effects of CD388 Injection exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.
- The subject or subject's partner, if consented, should be monitored until the postnatal day 28 or until termination of the pregnancy. The outcome should be reported using the Pregnancy Outcome or Abnormal Pregnancy Outcome form.

Pregnancy is not an AE, in and of itself. However, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.
A spontaneous abortion is always considered an SAE and will be reported as described in the AE and SAE sections. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to the Medical Monitor.

12. STATISTICAL METHODS

A Statistical Analysis Plan (SAP) will be prepared and finalized before unblinding for the first interim analysis. Any deviations from the final SAP will be described and justified in the study report. All statistical analyses will be performed using SAS®.

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables, will be provided. All data will be summarized separately by dose level and study drug (CD388 Injection or placebo). Listings of individual subject data will also be produced.

Safety, tolerability, and PK will be summarized using descriptive statistics. There will be no formal hypothesis testing.

12.1. Analysis Populations

Analysis populations are:

- Safety Population: all subjects who receive any amount of study drug
- PK Analysis Population: all subjects who receive CD388 Injection and who have any blood samples analyzed

12.2. Analysis of Study Population and Subject Characteristics

Demographics (including age, race, ethnicity, and gender), baseline assessments (including height, weight, and BMI), medical history, and administration of study drug will be summarized for the Safety Population.

12.3. Safety Analyses

Safety will be evaluated by presenting summaries of AEs and SAEs, ECGs, clinical laboratory evaluations (hematology, coagulation, serum chemistry, urinalysis), and vital signs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs and AESIs will be presented by System Organ Class (SOC) and Preferred Term (PT), relationship to study drug, and severity. A TEAE is defined as an AE that emerges during or after study drug administration having been absent pre-treatment, or worsens relative to the pre-treatment state, and through the final study visit. In addition, the incidence of serious TEAEs and TEAEs leading to discontinuation of study drug or from the study will be presented by SOC and PT.

Descriptive statistics for clinical laboratory test results, ECG parameters, and vital signs, and for changes from Baseline, will be presented by time point. The incidences of potentially clinically significant (PCS) clinical laboratory results, ECG parameters, and vital signs will also be summarized by time point.

A summary of the injection site evaluation will be presented. The number and percentage of subjects with any local reaction will be provided, as will the number and percentage of subjects with pain, tenderness, erythema/redness, and induration/swelling. The severity of each local reaction will also be presented.

12.4. Pharmacokinetic Analyses

Based on the individual plasma concentration-time data, using the actual sampling times (see Schedule of Events, Table 1), the following PK parameters will be included:

- maximum plasma concentration (C_{max})
- time to maximum plasma concentration (T_{max})
- terminal elimination half-life ($t_{½}$)
- apparent clearance (CL/F)
- apparent volume of distribution (V_Z/F)
- area under the plasma concentration-time curve from time 0 to time of last quantifiable sample ($AUC_{0\text{-last}}$)
- area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$)

CD388 concentration in the upper respiratory tract will also be determined.

Pharmacokinetic parameter estimation will be performed by non-compartmental analysis (NCA) with Phoenix® WinNonlin® version 8 or higher. The actual elapsed sampling times relative to dosing will be recorded during the study and will be used in the NCA analysis. Pharmacokinetic data handling and analysis will be further detailed in the SAP.

Descriptive statistics will be calculated for plasma concentrations at each individual time point and for all PK parameters. Mean and individual plasma concentration-time profiles will be presented graphically. Inferential statistics will also be conducted for log transformed PK exposure parameters versus historical control data in Western subjects from Study CD388.IM.SQ.1.01.

Pharmacokinetic samples for CD388 from this study may also be included in a population PK analysis, which will be reported separately.

12.5. Analyses of Pharmacogenomics, Exploratory Biomarkers, and Anti-Drug Antibodies

Analysis of the ADA results is to be determined and may include determination of the subject's positive/negative ADA status at baseline, treatment-emergent ADA in subjects with a negative baseline, as well as a post-baseline increase in titer for subjects with positive ADA at baseline.

Pharmacogenomics, and exploratory biomarkers will be reported separately.

12.6. Analyses of Respiratory Tract Infections

The number and percentage of subjects with any RTI will be provided.

12.7. Interim Analysis

After 50% of Cohort 1 subjects have completed study drug administration and have undergone protocol-specified procedures and assessments for ≥10 days, the Principal Investigator (PI)

and Sponsor will review blinded safety data: AEs (including systemic reactogenicity/injection site reactions, hypersensitivity reactions, and AESIs), vital signs, 12-lead ECGs, and clinical laboratory results (hematology, coagulation, serum chemistry, urinalysis) to determine the safety and tolerability of the study drug. The incidence and severity of AEs, and any adverse changes in vital signs, clinical laboratory findings, and ECGs will be considered when determining safety and tolerability of study drug. If the dose is determined to be safe and well tolerated ≥10 days after dosing, Cohort 2 will be enrolled. Enrollment of the remaining 50% of Cohort 1 will continue while the safety data of the first 50% of Cohort 1 is being reviewed. Similar processes will be followed for dose escalation from Cohort 2 to Cohort 3.

After the final subject of Cohort 2 has completed the Day 90 visit, Cohorts 1 and 2 may be unblinded for a formal interim data analysis. In addition, unblinded data reviews may occur as needed.

12.8. Determination of Study Sample Size

A total of 27 subjects will be enrolled in this study, with 21 of these subjects to receive CD388 Injection and 6 to receive placebo. The number of subjects was selected to allow sufficient evaluation of safety and tolerability, and PK, and is consistent with standards of practice for Phase 1 ethnic bridging studies.

12.9. Handling of Dropouts and Missing, Unused, and Spurious Data

Every effort will be made to collect all data at specified times. Handling of missing data will be detailed in the SAP.

12.10. Subject Disposition

Enrollment and discontinuations from the study will be summarized, including the reasons for discontinuation.

12.11. Deviation Reporting

Protocol deviations will be summarized. Protocol deviations are defined as any variation from the protocol, including enrollment of a subject who did not meet all inclusion and exclusion criteria and failure to perform the assessments and procedures within the required time frame.

13. INVESTIGATOR REQUIREMENTS

13.1. Protocol Adherence

The Investigator must adhere to the protocol as detailed in this document and agree that the Sponsor must approve any change to the protocol before seeking approval from the IRB/IEC. The Investigator will be responsible for enrolling only those subjects who have met the study selection criteria.

13.2. Electronic Case Report Forms

The contract research organization will make the eCRF accessible to authorized personnel over the internet from an electronic data capture (EDC) system used for the recording of study data as specified by this protocol. All eCRFs must be completed by trained study personnel. The Investigator is responsible for ensuring that the eCRF data are entered and completed in a timely manner.

Once all data queries and issues have been resolved for each subject, the Investigator will electronically sign each subject's eCRF to attest to the accuracy of the data.

13.3. Source Document Maintenance

Source documents are defined as documentation related to original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, study- or subject-specific e-mail correspondence, computer printouts, laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the Investigator and made available for inspections by the Sponsor and by regulatory authorities. The original signed ICF for each participating subject shall be filed with records kept by the Investigator, and a copy shall be given to the subject.

13.4. Study Monitoring Requirements

An authorized Sponsor representative will conduct site visits to inspect study data, subjects' medical records, and eCRFs in accordance with ICH guidelines, GCP, and the foreign regulations and guidelines, as applicable. A monitor will be utilized for monitoring ongoing drug accountability and adherence to protocol procedures.

The Investigator will allow representatives of the Sponsor and regulatory authorities to inspect facilities and records relevant to this study.

13.5. Study Completion

The Sponsor requires the following data and materials before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening throughout the study
- eCRFs (including data queries) properly completed by appropriate study personnel, signed and dated by the Investigator

- Copies of complete drug accountability records (drug inventory log and an inventory of returned or destroyed clinical material)
- Copies of protocol amendments and IRB/IEC approval and notification, if appropriate
- A summary of the study prepared by the Investigator (an IRB/IEC summary letter is acceptable)

End of Study Conduct, for the purpose of clinical trial registries, end of trial notifications to regulatory authorities and IRBs/ECs, will be the latest date on which the last visit in time of any study subject occurs.

14. QUALITY CONTROL AND QUALITY ASSURANCE

Written Standard Operating Procedures (SOPs) will be followed to ensure that the study is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Quality control will be applied to each stage of data handling. Regular monitoring, as defined in ICH GCP E6(R2), Section 1.38, "The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s)", will be conducted throughout the conduct of the study.

As defined in ICH GCP E6(R2), Section 5.18.1, the purpose of monitoring is to verify that:

- Rights and well-being of the human subjects are protected.
- The reported study data are accurate, complete, and verifiable from source documents.
- The conduct of the study is compliant with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements.
- Monitoring is an integral role in the quality control of a clinical trial and is designed to verify the quality of the study.

To fulfill the Quality Assurance requirements of GCP, audits will be conducted to assess and assure the reliability and integrity of a study's quality control systems and recognized standards.

As defined in ICH GCP E6(R2), Section 5.19, the purposes of an audit are to:

- Ensure subject safety
- Assure compliance to study protocol procedures, regulatory requirements, and SOPs
- Assure data quality

15. PROTECTION OF HUMAN SUBJECTS

This study will be conducted in compliance with the ICH Technical Requirements for Registration of Pharmaceuticals for Human Use E6(R2) Guideline for Good Clinical Practice, the ethical principles of the Declaration of Helsinki, FDA GCP guidelines, and any additional national or IRB/IEC-required procedures.

15.1. Informed Consent

This study will be conducted in compliance with ICH E6(R2) Guideline for Good Clinical Practice pertaining to informed consent. Subjects will give written consent to participate in the study at the first visit, prior to initiation of any study-related procedures, after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits. If a subject is unable to provide written informed consent, the subject's legally acceptable representative (i.e., acceptable to ICH and local law, as applicable) may provide written consent, as approved according to institution-specific guidelines. The ICF must be signed and dated by the subject, or the subject's legally acceptable representative, prior to study participation. A copy of the ICF must be provided to the subject or the subject's legally acceptable representative. If applicable, it will be provided in certified translation for non-English-speaking subjects. Signed ICFs must remain in the subject's study file and be available for verification by Sponsor at any time.

15.2. IRB/IEC Approval

This protocol, the ICF, and all relevant supporting data must be submitted to the IRB/IEC for approval. The protocol, ICF, and any advertisement used to recruit study subjects must be approved by the IRB/IEC. Approval by the IRB/IEC of the protocol and ICF must be obtained before the study may be initiated.

The Investigator is responsible for informing the IRB/IEC of any changes made to the protocol, and to advise them, at least once a year, about the progress of the study. The Investigator is also responsible for notifying the IRB/IEC of any significant AEs that occur during the study.

16. DATA HANDLING AND RECORD KEEPING

Training sessions, regular monitoring of Investigators by Sponsor-designated personnel, instruction manuals, data verification, crosschecking, and data audits will be performed to ensure quality of all study data. Investigator meetings may be performed to prepare Investigators and other study personnel for appropriate collection of study data.

The Sponsor will review and validate study data as defined in the monitoring plan.

It will be the responsibility of the Investigator to ensure that the essential documents are available at the study site. Any or all these documents may be subject to, and should be available for, monitoring by the Sponsor or inspection by the regulatory authorities as defined in the monitoring plan.

16.1. Direct Access to Source Data/Documentation

The Investigator agrees by his/her participation that the results of this study may be used for submission to national or international registration. If required, these authorities will be provided with the name of the Investigator and his or her address, qualifications, and extent of involvement. It is understood that the Investigator is required to provide Sponsor with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by any regulatory authorities, by the Sponsor and by the IRB/IEC as appropriate. At a subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Medical information obtained from subjects during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

16.2. Study Drug Accountability

All supplies of CD388 Injection/placebo required for completion of this study will be provided by the Sponsor. It is the responsibility of the unblinded Pharmacy or study staff to ensure that a current record of drug inventory and drug accountability is maintained. Inventory and accountability records must be readily available for inspection by the monitor and are open to inspection at any time by applicable regulatory authorities.

16.3. Retention of Records

Essential documents should be retained 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 have elapsed since the formal discontinuation of clinical development of the investigational product and shipment and delivery of the drug for investigational use is discontinued. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements of specific ICH and non-ICH countries, or by an agreement with the Sponsor. The Sponsor will inform the Investigator/institution as to when these documents no longer need to be retained.

16.4. Long-term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used for research related to influenza virus infection, flu-like disease, and safety, reactogenicity, and immunogenicity of CD388. They may also be used to develop tests/assays related to CD388 and influenza. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research.

17. FINANCING AND INSURANCE

The financing and insurance for this study are outlined in the Clinical Trial Agreement.

18. PUBLICATION POLICY

The data generated in this clinical study are the exclusive property of the Sponsor and are confidential. Authorship on any publication of the results from this study will be based on contributions to study design, enrollment, data analysis, and interpretation of results.

19. REFERENCES

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20. APPENDICES

APPENDIX 1. ACCEPTABLE METHODS OF CONTRACEPTION

An acceptable method of contraception includes one of the following:

- Abstinence from heterosexual intercourse
- Hormonal contraceptives (birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch)
- Intrauterine device (with or without hormones)
- A double barrier method (e.g., condom and spermicide)

APPENDIX 2. ECG AND VITAL SIGN ABNORMALITIES

Important abnormalities from the ECG readings are summarized below:

Abnormality	ECG Parameter			
	HR	**PR**	**QRS**	**QTcF**
Abnormalities on actual values				
Abnormally low	<45 bpm	NA	-	-
Abnormally high	≥120 bpm	>220 msec	≥120 msec	-
Borderline prolonged QT (males)	-	-	-	450 msec to ≤480 msec
Borderline prolonged QT (females)				470 msec to ≤480 msec
Prolonged QT	-	-	-	481 msec to ≤500 msec
Pathologically prolonged QT	-	-	-	>500 msec
Abnormalities on changes from baseline				
Normal QTcF change	-	-	-	<30 msec
Borderline QTcF change	-	-	-	30 msec to ≤60 msec
Abnormally high QTcF change	-	-	-	>60 msec

Abbreviations: bpm = beats per minute; HR = heart rate; NA = not applicable; PR = PR interval; QRS = QRS interval; QTcF = QT interval corrected for heart rate using Fridericia's formula.

Important abnormalities for vital signs are summarized below:

Abnormality	Vital Signs Parameter		
	HR	**DBP**	**SBP**
Abnormally low	≤45 bpm	≤50 mmHg	≤90 mmHg
Grade 1 or mild	-	>90 mmHg to <100 mmHg	>140 mmHg to <160 mmHg
Grade 2 or moderate	-	≥100 mmHg to <110 mmHg	≥160 mmHg to <180 mmHg
Grade 3 or severe	-	≥110 mmHg	≥180 mmHg
Abnormally high	≥120 bpm	-	-

Abbreviations: DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Fever [a]	38.0 to <38.6°C (100.4 to <101.5°F)	≥38.6 to <39.3°C (≥101.5 to <102.7°F)	≥39.3 to <40.0°C (≥102.7 to <104.0°F)	≥40.0°C (≥104.0°F)

a. Non-axillary temperatures only.

For tachypnea and hypoxia, refer to the grading scale in Table 7.

APPENDIX 3. DIAGNOSTIC CRITERIA AND MANAGEMENT FOR ANAPHYLAXIS

Diagnostic Criteria for Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, -tongue, -uvula)

   and **at least one** of the following:

   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

   c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that subject (minutes to several hours):

   a. Systolic blood pressure <90 mmHg or >30% decrease from that person's baseline

Management of Anaphylaxis

1. **Epinephrine:** When a subject meets any of the diagnostic criteria, the subject should receive epinephrine immediately, as it is the treatment of choice in anaphylaxis. Aqueous epinephrine, 0.01 mg/kg (maximum dose, 0.5 mg) administered intramuscularly every 5 to 15 minutes as necessary, is the recommended dosage for controlling symptoms and maintaining blood pressure. The 5-minute interval between injections can be liberalized to permit more frequent injections if deemed necessary by the clinician.
2. **Oxygen and adrenergic agonists:** High-flow oxygen (through a nonrebreather mask or endotracheal tube) should be administered to subjects experiencing respiratory symptoms or hypoxemia. Those who are hemodynamically unstable might benefit from oxygen as well. Inhaled β_2-agonists, such as albuterol, might be useful for bronchospasm refractory to epinephrine.

3. **Positioning of the subject:** Subjects in anaphylactic shock (i.e., those with anaphylaxis and signs of critical organ hypoperfusion) should be placed in a recumbent position with the lower extremities elevated unless precluded by shortness of breath or vomiting.
4. **Fluid resuscitation:** Subjects who remain hypotensive despite epinephrine should have aggressive fluid resuscitation. Large volumes of crystalloid might be needed in the first 5 to 10 minutes; in severe reactions with hypotension, up to 35% of the blood volume might extravasate in the first 10 minutes, and vasodilatation can cause pooling, with even more reduction in the effective blood volume and thus distributive shock.
5. **Vasopressors:** Potent vasopressors, such as noradrenaline, vasopressin, or metaraminol, might be required to overcome vasodilatation if epinephrine and fluid resuscitation have failed to maintain a systolic blood pressure of greater than 90 mmHg.
6. **H_1- and H_2-antihistamines:** Antihistamines (H_1- and H_2-antagonists) are slower in onset of action than epinephrine, have little effect on blood pressure, and should be considered a second-line treatment for anaphylaxis.
7. **Corticosteroids:** Because the onset of action is slow, steroids are not useful in the acute management stage. It has been suggested that their use might prevent a protracted or biphasic reaction.
8. **Glucagon for persistent hypotension in subjects taking β-blocker:** Theoretically, there are multiple mechanisms by which β-blockade could blunt the response to epinephrine. If administration of epinephrine in these subjects is ineffective, administration of glucagon can be attempted. Glucagon is thought to reverse refractory hypotension and bronchospasm by activating adenylate cyclase independent of the β-receptor; however, the occurrence and importance of this mechanism of action in anaphylaxis is unproved.
9. **Observation:** After the treatment of an anaphylactic reaction, an observation period should be considered for all subjects as the reaction might recur as the effect of epinephrine wears off (intramuscular epinephrine results in increased serum levels for an hour or more) and because of the risk of a biphasic reaction (1–72 hours after the acute reaction).

Source: Sampson 2006.

APPENDIX 4. RASH MANAGEMENT

For subjects reporting rash, the following should be performed:

All rashes will be discussed between the Investigator and the Sponsor, and in case of a causal relationship between the rash and the study drug, then the following visits and assessments will be performed as indicated below and in the "Visit Schedule for Rash Management" (see Appendix 5). Unscheduled follow-up visits for close follow-up of rash will be performed based on the grade (severity) of the rash. At the Investigator's discretion, additional visits and assessments may be performed.

The rash event should be captured in the AE section of the electronic case report form (eCRF), as well as in more detail in the specific rash assessment pages of the eCRF.

In case of rash, blood samples need to be collected for safety laboratory testing, and processed by the local laboratory. These samples need to be collected during the unscheduled visits as described below and in Appendix 5. A copy of the local laboratory reports should be anonymized and will be retrieved by the monitor.

The following parameters need to be tested: aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, erythrocyte sedimentation rate, and a complete blood cell count (including hemoglobin, hematocrit, red blood cell [RBC] count, white blood cell [WBC] count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).

Digital pictures need to be taken as described below and in Appendix 5. Digital pictures will be anonymized and stored on the Sponsor's secure server. Only the study team will have access to the pictures.

The subject may be treated symptomatically until the rash resolves. If the rash is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken, and the continuation of the subject in the study should be discussed with the Sponsor.

Dermatologist fees for evaluating subjects who experience a rash will be reimbursed by the Sponsor.

The following grades are based on the DAIDS Toxicity Grading Scale (DAIDS 2017) with adaptations made by the Sponsor:

Subjects should be informed that they should contact their doctor and visit the clinic immediately (unscheduled visit, day 1 of the rash) when they notice any rash.

Grade 1 Rash

A Grade 1 rash is defined as **erythema**.

- Subjects may continue the intake of study drug(s) (at the Investigator's discretion).
- An unscheduled visit for initial rash evaluation (day 1 of the rash) is required.
- Assessment of safety blood samples by the local laboratory is required. A copy of the local laboratory report should be anonymized and will be retrieved by the monitor.

- Digital pictures should be taken within 24 hours after the onset of the rash.
- Referral to a dermatologist is only needed if the rash diagnosis is uncertain (preferably within 24 hours after the onset of the rash). A copy of the dermatologist's report should be anonymized and will be retrieved by the monitor.
- Cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents may be prescribed.
- The description of the rash should be reported per 'Unscheduled Visit in Case of Rash' in the eCRF (i.e., the initial rash assessment pages).

For close follow-up of the rash, unscheduled visits will also be performed 1 and 7 days after the initial assessment of the rash. At these visits, safety blood samples and digital pictures should be taken. The follow-up rash assessment pages of the eCRF should be completed for all follow-up visits. For these and all subsequent local laboratory blood sample assessments: a copy of the local laboratory reports should be anonymized and will be retrieved by the monitor.

If the rash is unresolved after 7 days, additional unscheduled visits may be performed at the Investigator's discretion. Upon resolution/stabilization of the rash, digital pictures should be taken and the final rash assessment pages of the eCRF should be completed.

The subject should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops.

In case the rash evolves from a Grade 1 to a higher grade, additional unscheduled visits have to be conducted according to the guidelines for Grade 2 or Grade 3–4 rash, respectively.

Grade 2 Rash

A Grade 2 rash is defined as **diffuse, maculopapular rash OR dry desquamation**.

- Subjects will permanently discontinue the intake of study drugs and be withdrawn from the study. No rechallenge is allowed.

  Note: Subjects experiencing Grade 2 rash following the last intake of study drug may continue in the study as long as they are not re-exposed to suspect study drug.

- An unscheduled visit for initial rash evaluation (day 1 of the rash) is required.
- Assessment of safety blood samples by the local laboratory is required. A copy of the local laboratory report should be anonymized and will be retrieved by the monitor.
- Digital pictures should be taken within 24 hours after the onset of the rash.
- Referral to a dermatologist is required, preferably within 24 hours after the onset of the rash. A copy of the dermatologist's report should be anonymized and will be retrieved by the monitor.
- A biopsy is performed (preferably within 24 hours after the onset of the rash) if advised by the dermatologist. A copy of the biopsy report should be anonymized and will be retrieved by the monitor.
- Cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents may be prescribed.

- The description of the rash should be reported per 'Unscheduled Visit in Case of Rash' in the eCRF (i.e., the initial rash assessment pages).

For close follow-up of the rash, unscheduled visits will also be performed 1 and 7 days after the initial assessment of the rash. At these visits, safety blood samples and digital pictures should be taken. The follow-up rash assessment pages of the eCRF should be completed for all follow-up visits. For these and all subsequent local laboratory blood sample assessments: a copy of the local laboratory reports should be anonymized and will be retrieved by the monitor.

If the rash is unresolved after 7 days:

- And there is an increase in AST/ALT of 1 or 2 times the baseline value OR an increase in AST/ALT of less than 5 times the upper limit of normal (ULN), subjects should be followed weekly with repeated local lab assessments and digital pictures until resolution of the AST/ALT abnormalities.
- And there is no increase in AST/ALT, additional unscheduled visits (including local lab assessments and digital pictures) may be performed at the Investigator's discretion.

Upon resolution/stabilization of the rash, digital pictures should be taken and the final rash assessment pages of the eCRF should be completed.

The subject should be advised to contact the Investigator immediately if the rash fails to resolve (after more than 2 weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

In case the rash evolves from a Grade 2 to a Grade 3–4 rash, additional unscheduled visits must be conducted according to the guidelines for Grade 3–4 rash.

Grade 3 or Grade 4 Rash

A Grade 3 rash is defined as:

- **vesiculation, moist desquamation, or ulceration** OR
- **cutaneous event with one of the following** (revised by the Sponsor):
  - elevations in AST/ALT more than 2× baseline value and ≥5 × ULN
  - fever >38°C or 100°F
  - eosinophils >1000/mm^3
  - serum sickness-like reaction

A Grade 4 rash is defined as:

- **exfoliative dermatitis** OR
- **a generalized rash with mucous membrane involvement** OR
- **erythema multiforme** OR
- **Stevens-Johnson Syndrome** OR
- **rash associated with necrosis requiring surgery**

- Subjects will **permanently discontinue** the intake of all study drug(s) and be withdrawn from the study with Grade 3 or 4 rash identified. No rechallenge is allowed.
- An unscheduled visit for initial rash evaluation (day 1 of the rash) is required.
- Assessment of safety blood samples by the local laboratory is required on the day of initial rash evaluation and the day thereafter (days 1 and 2 of the rash), and as indicated below. A copy of the local laboratory report should be anonymized and will be retrieved by the monitor.
- Digital pictures should be taken within 24 hours after the onset of the rash and on day 1 of the rash, and as indicated below.
- Referral to a dermatologist is required, preferably within 24 hours after the onset of the rash. A copy of the dermatologist's report should be anonymized and will be retrieved by the monitor.
- A biopsy should be performed within 24 hours after the onset of the rash. A copy of the biopsy report should be anonymized and will be retrieved by the monitor.
- Appropriate management should be undertaken and subjects should be followed until resolution of the rash.
- The description of the rash should be reported per 'Unscheduled Visit in Case of Rash' in the eCRF (i.e., the initial rash assessment pages). The follow-up rash assessment pages of the eCRF should be completed for all follow-up visits.

<u>For close follow-up of the rash, unscheduled visits will be performed as follows:</u>

- Follow-up visits on days 2, 3, and 4 of the rash are required. Additional safety blood samples and digital pictures are to be taken on these days <u>only if</u> the subject's AST/ALT on day 1 <u>and/or</u> day 2 of rash >2× baseline value, and/or ≥5 × ULN and/or in case of rash progression. <u>For these and all subsequent local laboratory blood sample assessments:</u> a copy of the local laboratory report should be anonymized and will be retrieved by the monitor.
- A follow-up visit on day 6 of the rash is required and additional safety blood samples and digital pictures are to be taken regardless of the day 1/2 AST/ALT levels or rash progression.
- Thereafter, weekly follow-up visits are required (or more frequently at the Investigator's discretion) as long as Grade 3–4 rash is present. Once Grade 3–4 rash has resolved to Grade ≤2, follow-up should be performed according to the instructions for follow-up visits for Grade 1 or Grade 2 rash, respectively.
- As long as the rash remains Grade 3 or 4, additional safety blood samples and digital pictures are required at these weekly follow-up visits only if the subject's AST/ALT on day 6 of rash is still >2× baseline value and/or ≥5 × ULN and/or in case of rash progression, until resolution or stabilization of the AST/ALT elevations.

Upon resolution/stabilization of the rash, digital pictures should be taken and the final rash assessment pages of the eCRF should be completed.

Subjects should be advised to contact the Investigator immediately if they notice any worsening of the rash.

A complete summary of the guidelines for rash management is given in Appendix 5.

APPENDIX 5. VISIT SCHEDULE FOR RASH MANAGEMENT FOR ADULT SUBJECTS

This visit schedule summarizes the visits and assessments to be performed in case of rash. At the Investigator's discretion, additional visits and assessments may be performed. For all rashes, please also complete the specific rash assessment pages of the eCRF for all visits. Local laboratory blood sample assessments will be documented/collected as described in the text above.

	Grade 1 Rash	Grade 2 Rash	Grade 3 or 4 Rash
Rash day 1 [a]	• Study drug(s) **MAY** be **CONTINUED**. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures **REQUIRED** (within 24 h). • Referral to dermatologist **ONLY IF** rash diagnosis uncertain (within 24 h).	• Study drug(s) **MUST** be permanently **DISCONTINUED** if the subject has a persistent (i.e., >5 days with no response to treatment) Grade ≥2 [b] rash considered related to CD388 by the Investigator. Rechallenge is **NOT ALLOWED.** • Unscheduled visit for initial rash evaluation **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures **REQUIRED** (within 24 h). • Referral to dermatologist **REQUIRED** (within 24 h). • Biopsy **IF ADVISED** by dermatologist (within 24 h).	• Study drug(s) **MUST** be permanently **DISCONTINUED**. Rechallenge is **NOT ALLOWED**. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures **REQUIRED** (within 24 h). • Referral to dermatologist **REQUIRED** (within 24 h). • Biopsy **REQUIRED** (within 24 h).
Rash day 2	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures **REQUIRED.**	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures **REQUIRED.**	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures **REQUIRED.**
Rash day 3	No Rash follow-up visit required [c]	No Rash follow-up visit required [c]	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory and digital pictures **REQUIRED** only if on days 1 and/or 2 of rash AST/ALT >2× baseline value, AND/OR 5 × ULN, AND/OR in case of rash progression.
Rash day 4	No Rash follow-up visit required [c]	No Rash follow-up visit required [c]	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory and digital pictures **REQUIRED** only if on days 1 and/or 2 of rash AST/ALT >2× baseline value, AND/OR 5 × ULN, AND/OR in case of rash progression.

	Grade 1 Rash	Grade 2 Rash	Grade 3 or 4 Rash
Rash day 5	No Rash follow-up visit required [c]	No Rash follow-up visit required [c]	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **and** digital pictures **REQUIRED** only if on days 1 and/or 2 of rash AST/ALT >2× baseline value, AND/OR 5 × ULN, AND/OR in case of rash progression.
Rash day 6	No Rash follow-up visit required [c]	No Rash follow-up visit required [c]	• Follow-up visit **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures **REQUIRED.**
Rash day 7	No Rash follow-up visit required [c]	No Rash follow-up visit required [c]	No Rash follow-up visit required
Rash day 8	• Follow-up visit **REQUIRED** [c] • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures **REQUIRED.**	• Follow-up visit **REQUIRED** [c] • Assessment of safety blood sample by local laboratory **REQUIRED**. • Digital pictures **REQUIRED.**	No Rash follow-up visit required
Further Visits	If rash is unresolved after second follow-up visit, further visits (with local lab assessments and digital pictures) at the Investigator's discretion. [c]	If rash is unresolved after second follow-up visit: With AST/ALT increase ≤2× baseline value OR AST/ALT increase ≤5 × ULN: [c] • Weekly assessment of safety blood sample by local laboratory **REQUIRED** until resolution of AST/ALT abnormalities. • Weekly digital pictures **REQUIRED** until resolution of AST/ALT abnormalities. Without AST/ALT increase: further visits at the Investigator's discretion. [c]	• Weekly follow-up visits **REQUIRED** until resolution of Grade 3–4 rash to Grade ≤2 (further follow-up visits according to Grade 1 or Grade 2 rash instructions) • Weekly assessment of safety blood sample by local laboratory **and** digital pictures **REQUIRED** as long as Grade 3 or 4 rash is present but only if on day 6 of rash AST/ALT >2× baseline value, AND/OR 5 × ULN, AND/OR in case of rash progression, until resolution of AST/ALT abnormalities.
Upon Rash Resolution/ Stabilization [d]	Complete final rash assessment pages of the eCRF/eSource and take digital pictures.	Complete final rash assessment pages of the eCRF/eSource and take digital pictures.	Complete final rash assessment pages of the eCRF/eSource and take digital pictures.

a. Note that Day 0 of the rash is the first day of Investigator assessment and not the first day of rash as reported by the subject.
b. All grades in this list are per the DAIDS Toxicity Grading Scale (DAIDS 2017).
c. In case rash progresses from a Grade 1 or a Grade 2 to a higher grade, start follow-up schedule for Grade 2, 3, or 4 rash as appropriate.
d. Stabilization: to be agreed upon in collaboration with the Sponsor

APPENDIX 6. INVESTIGATOR SIGNATURE

I have read and understand Protocol CD388.SQ.1.03 and I agree to the following:

- To conduct the trial in compliance with GCP, with applicable regulatory requirement(s), with the protocol agreed to by the Sponsor and given approval/favorable opinion by the IRB/IEC
- To comply with procedures for data recording and reporting
- To permit monitoring, auditing, and inspection by the Sponsor, its designated representatives, and regulatory authorities
- To retain the essential documents in the Investigator/institution files until the Sponsor informs the Investigator or institution that these documents are no longer needed

INVESTIGATOR SIGNATURE

DocuSigned by:
David Kim, MD
Signer Name: David Kim, MD
Signing Reason: I approve this document
Signing Time: 14-Dec-2022 | 8:44:32 AM PST
FB75287A18B44714990613666AE1A8AE

14-Dec-2022

Investigator Signature | Date

David Kim, MD

Investigator Printed Name

Site Information

Site Number:	01229
Site Name:	Altasciences Clinical Los Angeles, Inc.
Site Address:	5630 Cerritos Avenue Cypress, CA 90630

DocuSign

Certificate Of Completion

Envelope Id: E29F400E70104117B194ECAEEEF2213B
Subject: CD388.SQ.1.03_Final Protocol_AM1_12-Dec-2022
Source Envelope:
Document Pages: 74
Certificate Pages: 3
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-08:00) Pacific Time (US & Canada)

Signatures: 2
Initials: 0

Status: Completed

Envelope Originator:
Joaquin Sosa
6310 Nancy Ridge Dr
STE 101
San Diego, CA 92121
jsosa@cidara.com
IP Address: 136.49.136.134

Record Tracking

Status: Original
12/13/2022 4:06:35 PM

Holder: Joaquin Sosa
jsosa@cidara.com

Location: DocuSign

Signer Events	Signature	Timestamp
Taylor Sandison, MD. MPH tsandison@cidara.com Chief Medical Officer Cidara Therapeutics Part 11 Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 032CF6C2-F867-4C8B-8C6E-30671D5BC544 Using IP Address: 192.124.167.250 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 12/13/2022 4:23:12 PM Viewed: 12/14/2022 7:56:14 AM Signed: 12/14/2022 7:56:55 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
David Kim, MD YKim@altasciences.com Principal Investigator Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: FB75287A-18B4-4714-9906-13666AE1A8AE Using IP Address: 208.127.236.214 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 12/14/2022 7:56:58 AM Viewed: 12/14/2022 8:42:43 AM Signed: 12/14/2022 8:44:36 AM
Electronic Record and Signature Disclosure: Accepted: 12/14/2022 8:42:43 AM ID: df255c43-8d38-4720-af2f-a92d6cdcaf56		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp
Margarita Ramos MRamos@altasciences.com Scientific Project Manager Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Accepted: 10/7/2022 8:31:31 AM ID: b9f1fd8d-dfe9-4114-bdf3-d08999ca89ee	COPIED	Sent: 12/14/2022 8:44:39 AM
Roni Martinez rmartinez@cidara.com Manager, Document Control Cidara Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	COPIED	Sent: 12/14/2022 8:44:40 AM Viewed: 12/14/2022 8:53:26 AM

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	12/13/2022 4:23:12 PM
Certified Delivered	Security Checked	12/14/2022 8:42:43 AM
Signing Complete	Security Checked	12/14/2022 8:44:36 AM
Completed	Security Checked	12/14/2022 8:44:40 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

By accepting this notice, I am documenting that I understand and approve the following:

1. When I sign documents or data electronically, I am accountable and responsible for all items thus signed.
2. I am to be held responsible for all actions initiated under my electronic signature.
3. I will use my electronic signature only for those assigned tasks that I have the education, training, and experience to perform.

I will comply with the US FDA 21 CFR Part 11 and EU Annex 11 security rules for Cidara Therapeutics use of electronic signatures as follows:

1. I will not share passwords and/or identification codes used to log into a system or to manifest an electronic signature for Cidara Therapeutics documents.
2. I will immediately notify Cidara Therapeutics of any loss of misuse of passwords and/or identification codes which may have been used to log into a system or to manifest an electronic signature for Cidara Therapeutics documents.