Study Protocol

Title: A proof-of-concept, randomized, double-blind, placebo-controlled, Phase 2a study to assess the prophylactic antiviral activity against influenza, safety, tolerability, and pharmacokinetics of CD388 via a human viral challenge model

NCT Number: NCT05523089

Document Date: 06 OCT 2022

CLINICAL STUDY PROTOCOL

A PROOF-OF-CONCEPT, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2A STUDY TO ASSESS THE PROPHYLACTIC ANTIVIRAL ACTIVITY AGAINST INFLUENZA, SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF CD388 VIA A HUMAN VIRAL CHALLENGE MODEL

Short Title:	Phase 2a study of the prophylactic antiviral activity of CD388 in an influenza challenge model in healthy adults
Version and Date of Protocol:	Final Version 4.0, 06Oct2022
Sponsor:	Cidara Therapeutics, Inc. 6310 Nancy Ridge Dr., Suite 101 San Diego, California 92121, USA
Sponsor Protocol Number:	CD388.SQ.2.02
hVIVO Protocol Number:	[redacted]
Compound Number:	CD388
IRAS ID Number:	1005986

Confidentiality and Protections Statement:

Sponsor Statement

This protocol, CD388.SQ.2.02, was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the study intervention, and with the moral, ethical, and scientific principles governing clinical research as set out in the current Declaration of Helsinki and the principles of International Council for Harmonisation (ICH) Good Clinical Practice (GCP).

Sponsor Signatory:

[redacted]

[redacted]

Date

(DD MMM YYYY)

Investigator Agreement:

I have read the protocol and agree to conduct the study in accordance with the approved protocol and any future amendments, the Declaration of Helsinki, the principles of ICH GCP, the current regulatory requirements as detailed in the Medicines for Human Use (Clinical Trial) Regulations (Statutory Instrument 2004/1031) and all subsequent amendments, the United Kingdom (UK) Data Protection Act 2018, any other applicable laws, and guidance.

I agree to conduct the procedures described in this protocol according to these guidelines and to appropriately direct and assist the study staff under my control.

Principal Investigator Signatory:

Name (typed or printed): [redacted]

Signature: _____ Date: _____

(DD MMM YYYY)

Note: In this protocol, the terms hVIVO and 'investigator' distinguish between the principal investigator's (PI's) responsibility, and actions required by the organisation (hVIVO). The term 'investigator' includes appropriately qualified persons to whom the PI has formally delegated his/her investigator roles and responsibilities.

Study Staff Contact Information

CONTACT	DETAILS
Sponsor	Cidara Therapeutics, Inc. 6310 Nancy Ridge Dr., Suite 101 San Diego, California 92121, USA [redacted] [redacted] [redacted] [redacted]
Sponsor's representative	[redacted] Cidara Therapeutics, Inc. 6310 Nancy Ridge Drive, Suite 101 San Diego, California 92121, USA [redacted] [redacted] [redacted]
Principal investigator and clinical study unit	[redacted] hVIVO Services Limited Queen Mary BioEnterprises Innovation Centre 42 New Road, London E1 2AX, United Kingdom (UK) [redacted]
Sponsor's medical expert/medical monitor	[redacted] Cidara Therapeutics, Inc. 6310 Nancy Ridge Dr., Suite 101 San Diego, California 92121, USA [redacted] [redacted]
Key protocol contributors	Refer to the local study contact list document

Table of Contents

List of Tables

List of Figures

1. Protocol Synopsis

Protocol Title	A proof-of-concept, randomised, double-blind, placebo-controlled, Phase 2a study to assess the prophylactic antiviral activity against influenza, safety, tolerability, and pharmacokinetics of CD388 via a human viral challenge model
Short Title	Phase 2a study of the prophylactic antiviral activity of CD388 in an influenza challenge model in healthy adults
Protocol number	[redacted]/CD388.SQ.2.02
Sponsor	Cidara Therapeutics, Inc.
Clinical phase	2a
Study site(s)	hVIVO Services Limited, Queen Mary BioEnterprises Innovation Centre, 42 New Road, London, E1 2AX United Kingdom (UK) hVIVO Services Limited The Whitechapel Clinic (formerly The Whitechapel Hotel) 43-53 New Road, London, E1 1HH UK
Study type	Interventional
Indication	Prevention of seasonal and pandemic influenza
Design	This is a proof-of-concept, randomised, double-blind, placebo-controlled, Phase 2a study of subcutaneously administered CD388 in an influenza human viral challenge model

Objectives and Endpoints

Objectives	Endpoints
Primary:	
Efficacy	
To evaluate the prophylactic efficacy of CD388 in terms of reduction of area under the viral load-time curve (VL-AUC) after influenza viral challenge when compared to placebo.	• VL-AUC of influenza challenge virus as determined by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) on nasal samples starting a day post viral challenge (Day 1, pm) up to Day 8 (am).

Secondary:	
Efficacy	
To evaluate the effect of CD388, in reducing or shortening viral shedding after influenza viral challenge compared to placebo.	• Peak viral load of influenza as defined by the maximum viral load determined by quantifiable qRT-PCR measurements in nasal samples from Day 1 (pm) up to Day 8 (am). • Time (hours) to confirmed negative test by quantifiable qRT-PCR measurements in nasal samples from Day 1 (pm) to first confirmed undetectable assessment after peak measure.
To evaluate the effect of CD388, in reducing or shortening culturable/replicating virus after influenza viral challenge compared to placebo.	• VL-AUC of influenza challenge virus as determined by viral culture on nasal samples, from Day 1 (pm) up to Day 8 (am). • Peak viral load of influenza as defined by the maximum viral load determined by quantitative viral culture measurements in nasal samples from Day 1 (pm) up to Day 8 (am). • Time (hours) to confirmed negative test by quantifiable viral culture measurements in nasal samples from Day 1 (pm) to first confirmed undetectable assessment after peak measure.
To evaluate the effect of CD388, in reducing clinical symptoms due to influenza viral challenge compared to placebo.	• Area under the curve over time of total clinical symptoms score (TSS-AUC) as measured by graded symptom scoring system collected 3 times daily from Day 1 (am) up to Day 8 (am). • Peak symptoms diary card score: peak of total clinical symptoms (TSS) as measured by graded symptom scoring system collected 3 times daily from Day 1 (am) up to Day 8 (am). • Peak daily symptom score: individual maximum daily sum of symptom score from Day 1 up to Day 8. • Time to symptom resolution as measured by graded daily symptom score system from time of peak daily symptom score to time of returning to baseline score.
To evaluate the effect of CD388, in reducing the incidence of influenza infection due to influenza viral challenge, compared to placebo.	• RT-PCR-confirmed influenza infection, defined as 2 quantifiable (≥ lower limit of quantification [LLOQ]) qRT-PCR measurements (reported on 2 or more independent samples over 2 days), from Day 1 (pm) up to Day 8 (am). • Occurrence of at least 1 positive quantitative (≥LLOQ) cell culture measurement in nasal samples, from Day 1 (pm) up to Day 8 (am). • RT-PCR-confirmed symptomatic influenza infection, defined as:

	○ RT-PCR-confirmed influenza infection (2 quantifiable [≥LLOQ] qRT-PCR measurements [reported on 2 or more independent samples over 2 days]), from Day 1 (pm) up to Day 8 (am), AND ○ Symptoms ≥2 at a single time point. • RT-PCR-confirmed moderately severe symptomatic influenza infection, defined as: ○ RT-PCR-confirmed influenza infection (2 quantifiable [≥LLOQ] qRT-PCR measurements [reported on 2 or more independent samples over 2 days]), from Day 1 (pm) up to Day 8 (am), AND ○ Any symptoms of grade ≥2 at a single time point. • Culture lab-confirmed symptomatic influenza infection, defined as: ○ Lab-confirmed culturable influenza infection (1 quantifiable [≥LLOQ] cell culture measurement), from Day 1 (pm) up to Day 8 (am), AND ○ Symptoms ≥2 at a single time point.
Safety	
To evaluate the safety of CD388 when compared to placebo.	• Occurrence of solicited adverse events (AEs) from subcutaneous dosing up to Day 0. • Occurrence of unsolicited AEs from subcutaneous dosing up to Day 28 (±3 days). • Occurrence of unsolicited AEs from subcutaneous dosing up to the final follow-up visit (Day 180 ±14 days).
Tertiary / Exploratory*:	
To further evaluate the effect of CD388, in reducing or shortening viral shedding after influenza viral challenge compared to placebo.	• Duration of quantifiable influenza qRT-PCR measurements in nasal samples from Day 1 (pm) up to Day 8 (am). Duration is defined as the time (hours) from first detectable until first confirmed undetectable assessment after their peak measure (after which no further virus is detected).
To further evaluate the effect of CD388, in reducing or shortening culturable/replicating virus after influenza viral challenge compared to placebo.	• Duration of quantitative influenza viral culture measurements in nasal samples from Day 1 (pm) up to Day 8 (am). Duration is defined as the time (hours) from first detectable until first confirmed undetectable assessment after their peak measure (after which no further virus is detected).

To further evaluate the effect of CD388, in reducing clinical symptoms due to influenza viral challenge compared to placebo.	• Time to peak as measured by graded daily symptom score system (from Day 1 [am] to the time of peak daily symptom score). • Number (%) of participants with symptom scored grade 2 or higher, from Day 1 (am) up to Day 8 (am). • Number (%) of participants with symptom scored grade 2 or higher by time point, from Day 1 (am) up to Day 8 (am).
To further evaluate the effect of CD388, in reducing the incidence of influenza infection due to influenza viral challenge, compared to placebo.	• Number (%) of participants with lab-confirmed infection and fever (≥37.9°C). • Further sensitivity analysis may be performed on the above qRT-PCR-related incidence endpoints where detection by qRT-PCR is reported above the lower limit of detection (LLOD) instead of the LLOQ. Details will be provided in the statistical analysis plan (SAP).
To evaluate the effect of CD388, in reducing nasal discharge compared to placebo.	• Total weight of mucus produced from Day 1 (am) up to Day 8 (am). • Total number of tissues used by participants from Day 1 (am) up to Day 8 (am).
To evaluate the effect of CD388, in reducing incidence of community-acquired influenza infection compared to placebo.	• Laboratory--confirmed symptomatic influenza infection (community acquired), defined as: ○ Self-reported influenza-like symptoms, AND ○ Community acquired (not challenge virus) laboratory-confirmed influenza infection PCR measurement and/or lateral flow positive, or other equivalent) reported on any occasion from discharge from quarantine up to Day 90 and/or up to Day 180 (±14 days).
To monitor the safety of the challenge virus.	• Occurrence of unsolicited AEs from virus challenge (Day 0) up to Day 28.
To evaluate the plasma PK of CD388.	• Pharmacokinetic (PK) parameters following CD388 administration will be determined as appropriate from the available data including: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration-time curve from time 0 to time of last quantifiable sample (AUC_{0-t}), and area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$).
To explore CD388 concentrations in nasopharyngeal swab samples.	• CD388 concentrations in nasopharyngeal swabs.

To explore PK/PD of CD388.	• Plasma concentration at specific time points, or PK parameters across dose groups, will be compared to viral or symptomatic endpoints in an effort to characterise the exposure response of CD388, and will be reported separately.
To explore cytokines and chemokines in nasal samples.	• Cytokine/chemokine levels may be explored in nasal samples, related to CD388 and infection.
To explore cytokines and chemokines in serum samples.	• Cytokine/chemokine levels may be explored in serum samples, related to CD388 and infection.
To explore markers associated with the effect of CD388 or with infection.	• Gene expression (messenger RNA [mRNA]) in whole blood.
To explore viral resistance markers in influenza viral positive nasal samples	• Viral resistance markers relevant for CD388.

*Note that tertiary objectives and endpoints are optional and might be assessed only if needed; therefore, not all testing might be performed and reported.

Hypothesis	The primary statistical hypothesis is that prophylactic treatment with CD388 at the dose of 150 mg will significantly reduce influenza VL-AUC as determined by qRT-PCR on nasal samples compared to placebo
Investigational medicinal product (IMP)	Active: CD388 liquid for subcutaneous injection Placebo: sterile normal saline for injection
Challenge agent	Influenza H3N2 A/Perth/16/2009
Challenge agent route	Intranasally
Challenge agent titre	~$10^{5.5}$ tissue culture infective dose (50%) ($TCID_{50}$)
Study population	Healthy adult male and female participants aged between 18 to 55 years, inclusive, with a total body weight ≥50 kg and body mass index (BMI) ≥18 kg/m^2 and ≤35kg/m^2, who have been determined to be sero-suitable with regard to pre-existing antibody levels to the influenza challenge virus.
Summary of study design	This is a single-centre, randomised, double-blind, placebo-controlled, proof-of-concept study in healthy adult male and female participants 18 to 55 years of age, inclusive. The primary goal of this Phase 2a study is to assess the prophylactic antiviral activity against influenza, safety, tolerability, and PK of CD388 via a human viral challenge (HVC) model, and to explore the impact of dose levels on efficacy. Each participant will receive a single administration of CD388 or placebo; multiple dose levels of CD388 may be evaluated.

	A total of up to 168 participants is planned to be enrolled in this study in up to 2 cohorts. Cohort 1 will consist of up to 90 participants that will be enrolled simultaneously; a placebo arm (Arm 1, n=up to 30) and two CD388 dose arms (Arm 2 [150 mg CD388, n= up to 30] and Arm 3 [50 mg CD388, n= up to 30]). Cohort 2 details will be confirmed further to interim analyses as described below. Cohort 2 may include extension of the arms in Cohort 1 or include additional dose levels not exceeding 150 mg. A first interim analysis will be performed for participants in Cohort 1 who have completed the inpatient phase at the time the interim analysis is performed. An optional second interim analysis may be performed within Cohort 2, depending on the outcome of the first interim analysis. Each interim analysis will inform on: • The final participant numbers per study arm. • The CD388 dose levels to be studied. • The number of CD388 dose levels to be studied. Participants will receive IMP (CD388/placebo) prior to being inoculated with the influenza challenge virus and will undergo assessments as per Schedule of Events (SoE). The timing of administration of CD388 or placebo is chosen so as to approximate T_{max} of CD388 in plasma at the time of challenge virus inoculation. In these cases, the timing of procedures and the admission day to quarantine would be altered accordingly. The study is divided into the following phases: **Screening Phase**: from Day -96 to Day -7/-6 quarantine admission. Historical generic screening data collected through the hVIVO generic screening process may be transferred to this study after the study-specific consent form has been signed by the participant. **Inpatient Phase**: Participants will be resident in the quarantine unit for approximately 16 days (from Day -7/-6 to Day 8). Procedures will include: • **Pre-HVC:** ○ Admission to quarantine unit on Day -7/-6. ○ Baseline assessments and randomisation will be conducted as per SoE up to Day -5, pre-dose. ○ Administration of CD388 or placebo on Day -5. • **HVC:** ○ Influenza virus inoculation on Day 0. • **Post-HVC:** ○ Day 1 onwards and each day – study assessments will be conducted as per SoE. ○ Participants will be discharged from the quarantine unit on Day 8 (or may remain longer at the principal investigator's [PI's] discretion). **Outpatient Phase:** • Follow-up visit(s): Day 17 (±1 day), Day 28 (±3 days), Day 60 (±7 days), and Day 120 (±14 days).

	• Final visit: Day 180 (±14 days).
Randomisation	In Cohort 1, the randomisation number encodes the participant's assignment to 1 of 3 study arms: placebo (Arm 1, n= up to 30) and two CD388 dose arms (150 mg CD388 [Arm 2, n= up to 30] and 50 mg CD388 [Arm 3, n= up to 30]). The initial randomisation schedule used varying block sizes (12 and 3) and 2 sets of randomisation ratios (4:5:3 and 1:0:2) to facilitate achieving the targeted sample sizes for the interim analysis. This was updated as per Non-Substantial Amendment 03 to a 1:1 randomisation between Arm 1 and Arm 2 until the first interim analysis.
Participant replacement policy	Participants may be replaced in this study. [redacted]
Expected duration of participation per participant	Approximately 9 months from screening to the participant's last scheduled visit.
Overall duration of clinical phase	The length of the clinical phase is expected to be approximately 19 months from first participant's planned first study visit (screening visit) to the last participant's last scheduled study visit.
End of study	The end of the study is defined as the date of the last follow-up of the last participant in the study.
Sample size determination	A total sample size of 168 participants is estimated to be sufficient to achieve the objectives of this study. Depending on recruitment, the number enrolled at the planned first interim analysis is expected to be up to 30 participants in Arm 1 (placebo),Arm 2 (150 mg CD388), and Arm 3 (50 mg CD388). An example of sample size estimates for the interim analysis depending on the recruited number of subjects is shown below: • The sample size of 30 participants per arm will have 95% power to detect a statistically significant difference between groups, using a Wilcoxon rank-sum test with a one-sided type-1 error rate of 0.025, assuming that the probability that the VL-AUC for a participant in Arm 2 (150 mg CD388) is less than the VL-AUC for a participant in Arm 1 (placebo) is 0.75.

Probability (AUC_{CD388} < $AUC_{Placebo}$)	**0.60**	**0.65**	**0.70**	**0.75**	**0.80**
Power at Interim analysis					

	Interim analysis Arm 1 n=30 vs Arm 2 n=30	0.259	0.515	0.785	0.951	0.996

Statistics

Primary efficacy analysis

The primary endpoint (VL-AUC of the influenza challenge virus as determined by qRT-PCR on nasal samples [virology]), will be analysed on the per protocol (PP) analysis set.

The PP set will consist of all participants randomised, having received IMP (CD388/placebo), challenged with the study virus, who have a valid result for at least 80% of the planned qRT-PCR nasal samples from Day 1 (pm) up to Day 8 (am), i.e., at least 11 out of 14, and present no major deviations likely to impact the evaluation of the primary efficacy endpoint. All deviations and cases with at least 1 qRT-PCR result missing will be reviewed during the blinded data review meeting and adjudicated as belonging to the PP set or not.

The calculation of the VL-AUC will be performed on $\log_{10}$-transformed PCR data using the trapezoidal summation rule based on actual time intervals in hours.

Descriptive statistics for the mean and median and the 2-sided 95% confidence interval (CI) for the mean will be presented by study arm. The significance of the difference between each CD388 arm and the placebo arm will be analysed using the Wilcoxon rank-sum test. The estimator of the difference in area under the curve (AUC), with 95% CI will be obtained via the Hodges-Lehman (+Moses) method. The one-sided p-value will be presented. No adjustment of the type-1 error rate for multiple comparisons will be performed and each test will use a nominal level of 0.025 1-sided.

The analysis will be repeated on the ITT analysis set as a sensitivity analysis.

Interim analysis

A first interim analysis will be performed, by an unblinded team not involved in daily management of the study, for participants in Cohort 1 who have completed the inpatient phase at the time the interim analysis is performed. An optional second interim analysis may be performed within Cohort 2, depending on the outcome of the first interim analysis. Summary results of each interim analysis will inform on:

- The participant numbers per study arm.
- The CD388 dose levels to be studied.
- The number of CD388 dose levels to be studied. The SAP will describe the planned interim analyses in greater detail.

1.1. Study Schematic: On-study Participant Progression

SCREENING PHASE	INPATIENT PHASE: QUARANTINE/ISOLATION, DOSING, AND HUMAN VIRAL CHALLENGE					OUTPATIENT PHASE
Day -96 to Day -7/-6 Screening*	Day -7/6 to Day -5, pre-dose Admission to quarantine unit, baseline assessments & randomisation	Day -5 Subcutaneous dosing with CD388 or placebo	Day 0 Influenza virus inoculation	Days 1 to 7 Assessments as per Schedule of Events	Day 8 Discharge from quarantine unit**	Follow-up visits: Day 17 (±1 day), Day 28 (±3 days), Day 60 (±7 days), and Day 120 (±14 days) Final visit: Day 180 (±14 days)

NOTES:

[redacted]

[redacted]

1.2. Schedule of Events

Study Phase ➔	Screening Phase*	Inpatient Phase (Quarantine Isolation and Human Viral Challenge [HVC])																Outpatient Phase					Early Withdrawal Visit
		Admission to quarantine		Dosing with CD388					HVC			Post-HVC							Discharge	Follow-up Clinic Visits				
Study Day # ➔	Day-96 to Day -7/-6	D-7	D-6	D -5 (dosing)	D-4	D-3	D-2	D-1	D0			D1	D2	D3	D4	D5	D6	D7	D 8	D17 (±1 day)	D28 (±3 days)	D60 (±7 days)	D120 (±14 days)	D180 (±14 days)	Quarantine post challenge
Procedure ➔									Pre-HVC	HVC	Post-HVC														
Eligibility criteria (+)	X	[redacted]																							
Written consent (b)	X																								
Medical & medication history	X																								
Demographics	X																								
Height & weight, body mass index (BMI) (c)	X																								
Patient Health Questionnaire-9 (PHQ-9)	(X)																								
Generalised Anxiety Disorder Questionnaire-7 (GAD-7)	(X)																								
Alcohol breath test	X																								
Urinalysis (d)	X																								
Urine drugs of misuse and nicotine screen	X																								
Urine pregnancy test	X																								
Complete physical examination	X																								
Symptom-directed physical examination																									
Vital signs (heart rate, respiratory rate, systolic and diastolic blood pressure, peripheral oxygen saturation [SpO_2]) (e)	X																								

Study Phase ➔	Screening Phase*	Inpatient Phase (Quarantine Isolation and Human Viral Challenge [HVC])																Outpatient Phase				Early Withdrawal Visit
		Admission to quarantine		Dosing with CD388					HVC			Post-HVC							Discharge	Follow-up Clinic Visits				
Study Day # ➔	Day-96 to Day -7/-6	D-7	D-6	D -5 (dosing)	D-4	D-3	D-2	D-1	D0			D1	D2	D3	D4	D5	D6	D7	D 8	D17 (±1 day)	D28 (±3 days)	D60 (±7 days)	D120 (±14 days)	D180 (±14 days)	Quarantine post challenge
Procedure ➔									Pre-HVC	HVC	Post-HVC														
Tympanic temperature (e)	X	[redacted]																							
Symptom diary card (e)																									
24-hour tissue count & nasal discharge weight (g)																									
Spirometry (h)	X																								
12-lead electrocardiogram (ECG)	X																								
Respiratory Tract Infection Surveill																									
Weekly 7-day recall diary card (i)																									
Nasal/throat swab self-collection (j)																									
Product Administration																									
Randomisation																									
Investigational medicinal product (IMP; CD388/placebo) dosing																									
Reactogenicity diary card (k)																									
Challenge virus inoculation																									
Collection Of Blood Samples																									
Serum follicle-stimulating hormone (FSH) (postmenopausal women)	X																								
Serum β-human chorionic gonadotrophin (β-HCG) pregnancy test (all females)																									

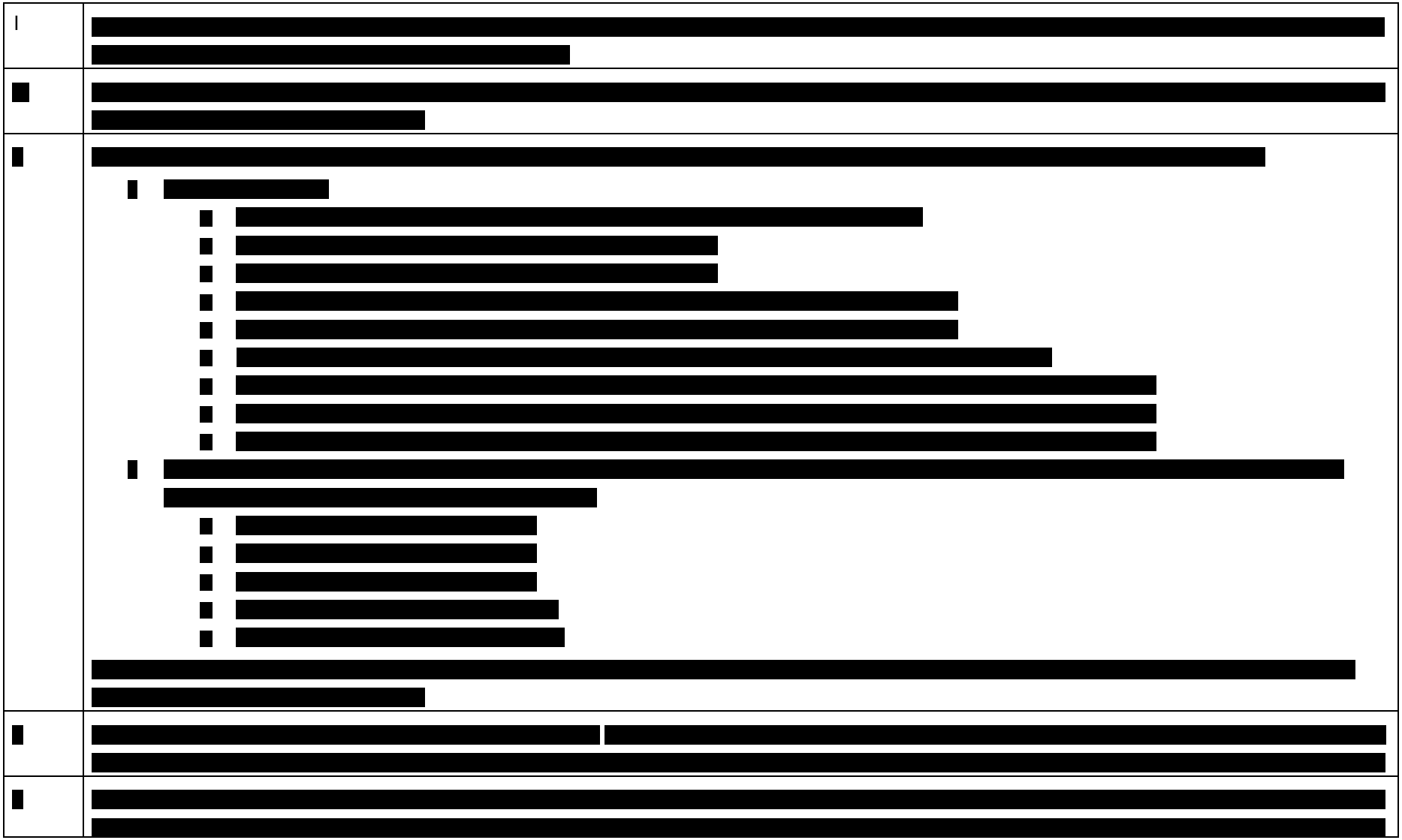
Study Phase ➔	Screening Phase*	Inpatient Phase (Quarantine Isolation and Human Viral Challenge [HVC])																Outpatient Phase					Early Withdrawal Visit
		Admission to quarantine		Dosing with CD388					HVC			Post-HVC							Discharge	Follow-up Clinic Visits				
Study Day # ➔	Day-96 to Day -7/-6	D-7	D-6	D -5 (dosing)	D-4	D-3	D-2	D-1	D0			D1	D2	D3	D4	D5	D6	D7	D 8	D17 (±1 day)	D28 (±3 days)	D60 (±7 days)	D120 (±14 days)	D180 (±14 days)	Quarantine post challenge
Procedure ➔									Pre-HVC	HVC	Post-HVC														
Human immunodeficiency virus (HIV) & hepatitis serology	X	[redacted]																							
Haematology (l)	X																								
Biochemistry (l)	X																								
Coagulation	X																								
Thyroid function test	X																								
Cardiac enzymes	X																								
Blood – serum markers humoral immunity (m)	X																								
Blood – serum proteomics (cytokine/chemokine) (n)																									
Blood PAXgene for transcriptomics																									
Blood – plasma pharmacokinetics (PK) (n)																									
Blood – serum anti-drug antibodies (ADA)																									
Blood – PAXgene DNA for pharmacogenomics																									
Collection Of Respiratory Samples																									
Nasopharyngeal swab – Respiratory pathogen screen including SARS-Cov-2 (e.g., Biofire) (o)																									

Study Phase ➔	Screening Phase*	Inpatient Phase (Quarantine Isolation and Human Viral Challenge [HVC])																Outpatient Phase					Early Withdrawal Visit
		Admission to quarantine		Dosing with CD388					HVC			Post-HVC							Discharge	Follow-up Clinic Visits				
Study Day # ➔	Day-96 to Day -7/-6	D-7	D-6	D -5 (dosing)	D-4	D-3	D-2	D-1	D0			D1	D2	D3	D4	D5	D6	D7	D 8	D17 (±1 day)	D28 (±3 days)	D60 (±7 days)	D120 (±14 days)	D180 (±14 days)	Quarantine post challenge
Procedure ➔									Pre-HVC	HVC	Post-HVC														
Nasopharyngeal swab – viral discharge test				[redacted]																					
Nasopharyngeal swab for virology and exploratory purposes (qRT-PCR & culture, CD388) (p)																									
Nasosorption for cytokine/chemokine (q)																									
Safety Assessments																									
Adverse event recording (r)		Continuous																							
Concomitant medications (r)		Continuous																							

KEY NOTES FOR TIME AND EVENTS SCHEDULE

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

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]s that occurred over the last week. Participants will [redacted]
[redacted]	[redacted]
[redacted]	[redacted]



[redacted]

2. Introduction

CD388 is a zanamivir-crystallisable fragment (Fc) conjugate. Zanamivir is a small molecule antiviral (neuraminidase inhibitor [NAI]). CD388 is being developed for the prevention of seasonal and pandemic influenza.

2.1. Influenza

Influenza viruses are associated with significant human disease and cause annual epidemics during autumn and winter. Although most people recover from seasonal influenza within 1 to 2 weeks without requiring medical attention, globally, millions are hospitalised each year and about 650,000 deaths occur due to influenza (Iuliano et al, 2018), particularly among the very young, elderly, and chronically ill. In the United States (US), an estimated 37.4 – 42.9 million symptomatic influenza-related illnesses, 17.3 – 20.1 million influenza-related medical visits, 531,000 – 647,000 influenza-related hospitalisations, and 63,400 – 61,200 deaths occurred during the 2018–2019 influenza season (Xu et al, 2019). Comparable mortality and morbidity rates have been reported for European countries. These numbers remain high year after year because currently no effective medicine is available for the prevention of influenza. Currently, the influenza type A viruses H1N1 and H3N2 are circulating in humans, along with influenza type B viruses. H3N2 viruses have been predominant in most seasons and have caused a higher number of deaths and hospitalisations than H1N1 and influenza B viruses (Nunes et al, 2011; Thompson et al, 2004; Zucs et al, 2005).

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 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.

The influenza human challenge model was established to not only aid understanding of influenza disease and transmission, but to also assess the efficacy of antivirals, immunomodulators, and vaccines (as reviewed by Lambkin-Williams et al, 2018; Yogaratnam et al, 2019; Bueno de Mesquita et al, 2021; Nguyen-Van-Tam et al, 2020; Ramos-Sevillano et al, 2019). hVIVO has given different influenza strains to over 1300 participants over the last 20 years. The influenza H3N2 A/Perth/16/2009 challenge strain used in the majority of studies to date has been given to over 350 healthy participants by hVIVO. The virus has been well tolerated with no virus-related serious adverse events (SAEs) occurring in any of the participants inoculated to date. Furthermore, the challenge virus has been shown to induce measurable disease profiles with clear distinction from non-infected participants and study participants have approximately 60% to 75% chance of becoming infected following the administration of the virus. Typical influenza illness is characterised by an abrupt onset of rhinitis, nasal stuffiness, fever, malaise, myalgia (muscle aches), and sore throat. In healthy adults, the illness usually resolves without any treatment, with relief of symptoms occurring naturally within 3 to 5 days. The disease profiles of the challenge agent are consistent with the mild to moderate disease profiles expected with wild-type challenge viruses in healthy adult participants (Fragaszy et al, 2017). In summary, the influenza H3N2 A/Perth/16/2009 challenge virus is considered safe,

well tolerated, and induces appropriate disease pathogenesis to be an effective viral challenge agent in the human viral challenge (HVC) studies.

2.2. 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 generated conjugates comprising multiple copies of a highly potent small molecule antiviral agent (the marketed NAI zanamivir) with a modified Fc domain that replace the variable domains in monoclonal antibodies. The small molecule targeting groups selectively engage a small, conserved pocket on the viral surface, which is not feasible with monoclonal antibodies. This molecule, CD388, is a first in class long-acting antiviral Fc-conjugate combining a surface-acting antiviral agent with the Fc of a human immunoglobulin G1 (IgG1) antibody.

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

- In traditional antibody-drug conjugates the drug is attached to full length human IgG (Fc + antigen-binding fragment); 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.

2.2.1. 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 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 as well as drug-resistant influenza strains. In vitro studies to characterise the extent of neonatal Fc receptor and Fc-γ receptor binding across different species were conducted. In vitro studies to characterise 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 targeting molecules’ compound alone was quantitatively tested at 37℃ in phosphate-buffered saline, plasma, and liver microsomes. Stability of the intact Fc-conjugated molecule, CD388, was qualitatively observed in liver microsomes at 37℃. In vivo, the pharmacokinetics (PK) were investigated in animal species that were used to characterise the pharmacological and toxicological profile of CD388 and related molecules; namely in mouse, rat, and monkey. More importantly, following PK studies in the mouse, rat, and monkey, plasma concentrations were quantified by a neuraminidase (NA)-capture or Fc-capture with Fc-detection enzyme-linked immunoassay (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 and/or subcutaneous 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 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.

2.2.2. Clinical Experience

A Phase 1, randomised, double-blind, single-dose and repeat single-dose, dose-escalation study to determine the safety, tolerability, and PK of CD388 intramuscular or subcutaneous administration in healthy subjects (Protocol CD388.IM.SQ.1.01) is currently ongoing. A blinded summary of CD388 clinical safety and tolerability results is provided below.

For this evaluation, clinical safety data (adverse events [AEs], vital signs, safety electrocardiograms [ECGs], laboratory evaluations) was cleaned and soft locked in 22 healthy subjects who received a dose of 50 mg or 150 mg of subcutaneous CD388, or placebo through at least 14 days post dose. The breakdown of subjects by treatment is shown in Table 2-1, along with the maximum duration post dose total duration included in this analysis.

Table 2-1: Duration of post-dose observations included in current blinded safety summary

Dose (mg)	Subcutaneous			
	Cohort	CD388	Placebo	Last Day/Visit Included in Softlock
		(n = 16)	(n =6)	
50	Cohort 1B (sentinel)	1	1	Day 45
50	Cohort 1B (main)	7	2	Day 30
150	Cohort 2B (sentinel)	1	1	Day 25
150	Cohort 2B (main)	7	2	Day 14

The percentage of all subjects who experienced at least one TEAE was 45.5%.

All treatment-emergent adverse events (TEAEs) were mild-moderate in severity and all, but one had resolved by the time of this report. The most frequent TEAE is headache of grade 1 or grade 2 in severity in 27.3% subjects. All AEs in the higher dose group (150 mg) were grade 1. There were no SAEs observed and no drug related TEAEs resulting in clinically significant haematology or clinical chemistry laboratory abnormalities. In addition, there were no safety issues related to ECGs, vital signs, or physical examination findings including local injection site reactions.

Blinded TEAEs by system organ class (SOC) and preferred term (PT) are presented in Table 2-2.

Table 2-2: Blinded treatment-emergent adverse events by system organ class and preferred term in the safety population

System Organ Class (SOC) Preferred Term (PT)	Total Subjects (N=22) n (%)
Number of subjects with at least one treatment-emergent adverse event (TEAE)	10 (45.5)
Ear and labyrinth disorders	1 (4.5)
Cerumen impaction	1 (4.5)
Gastrointestinal disorders	5 (22.7)
Constipation	3 (13.6)
Diarrhoea	3 (13.6)
Faeces hard	1 (4.5)
Nausea	1 (4.5)
Saliva discolouration	1 (4.5)
Vomiting	2 (9.1)
General disorders and administration site conditions	1 (4.5)
Non-cardiac chest pain	1 (4.5)
Infections and infestations	1 (4.5)
Upper respiratory tract infection	1 (4.5)
Nervous system disorders	7 (31.8)
Dizziness	1 (4.5)
Headache	6 (27.3)
Presyncope	1 (4.5)
Somnolence	1 (4.5)
Skin and subcutaneous tissue disorders	1 (4.5)
Acne	1 (4.5)
Dermatitis contact	1 (4.5)

A TEAE is defined as an AE that occurs during or after study drug administration.
A subject with multiple AEs within an SOC or PT is counted only once.

System Organ Class (SOC) Preferred Term (PT)	Total Subjects (N=22) n (%)
Percentages are calculated using the number of subjects in the safety population. MedDRA Version 24.1 was used for reporting AEs.	

Based on blinded safety results from the ongoing study following single subcutaneous administration of 50 and 150 mg CD388, these doses appear to be well tolerated. A decision was made and approved by the study Institutional Review Board to dose escalate to a higher subcutaneous dose of 450 mg with the next cohort.

2.3. Study Rationale

This is a proof-of-concept study to determine the prophylactic antiviral activity of a single subcutaneous administration of CD388 against experimental influenza infection and to confirm its safety, tolerability, and PK in a healthy adult population inoculated with the influenza H3N2 A/Perth/16/2009 challenge strain. Due to the current epidemiological situation with very low influenza incidence worldwide, it is challenging to demonstrate proof of concept of therapeutic or prophylactic efficacy of anti-influenza compounds in a natural infection setting. The HVC model offers a setting that is independent of the number of influenza cases at a given time. Also, this model has a track record of safety and has demonstrated proof-of-concept efficacy for numerous antiviral compounds and vaccines that were later found to be also efficacious in larger clinical studies in the setting of natural infection. It is important to establish proof of concept and minimally effective concentrations in this study in order to better design studies to establish the safety and efficacy of CD388.

Influenza challenge strains have been used for over 20 years by both hVIVO and others and have helped assess numerous antiviral, immunomodulating, and vaccine therapies. Specifically, hVIVO have safely and successfully used the influenza H3N2 A/Perth/16/2009 challenge strain in over 350 healthy participants (18 to 64 years of age).

2.4. Benefit/Risk Assessment

2.4.1. Risk Assessment

The potential risks to participants are detailed in Table 2-3. However, there may also be risks that are unforeseen and unanticipated (e.g., unknown allergies). Every effort will be made to monitor the health of the participants to ensure that such risks are minimised. Trained medical staff and appropriate facilities will be available to provide medical emergency care.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of CD388 may be found in the Investigator's Brochure.

Table 2-3: Risk Assessment

Potential Risk of Clinical Significance	Description of Risk	Mitigation Strategy
Study Intervention		
Subcutaneous dosing with CD388	There are no studies completed with CD388 in humans. Refer to Section 2.2.2, Clinical Experience, for a summary of results of an ongoing study. However, the study drug was tested in animals. In studies with rats and monkeys CD388 had no significant effect on the body weight, food consumption, heart activity, blood tests, urine tests, respiration, eye tests and other clinical tests conducted on the animals. Risks relating to procedure of administration of product: pain at site of administration, bruising at site, introduction of infection.	Participants will be closely monitored by clinical staff for any AEs after dosing and throughout the study as per the Schedule of Events (SoE). Administration will only be carried out by trained professionals with thorough cleaning of the area beforehand with alcohol wipes and the use of aseptic technique throughout.
Subcutaneous dosing with sterile normal saline (placebo)	Given that the placebo is a pharmacologically inert material, there should be no risk in relation to the product being administered. Similar risks apply to the procedure of administration: pain, bruising, introduction of infection into the skin.	Administration will only be carried out by trained professionals with thorough cleaning of the area beforehand with alcohol wipes and the use of aseptic technique throughout.
Pregnancy and birth control	Unknown.	Female participants of childbearing potential must use 1 form of highly effective contraception. Use of hormonal contraception should start at least 2 weeks prior to the first study visit. The contraception use must continue until 5 effective half-lives after the last dose of investigational medicinal product (IMP).

Potential Risk of Clinical Significance	Description of Risk	Mitigation Strategy
		Females who are pregnant or have been pregnant within 6 months prior to the study, and females who are breastfeeding, will be excluded from the study. Male participants must agree to the contraceptive requirements as described in Inclusion Criterion #7 from entry into quarantine and continuing until 5 effective half-lives after the last dose of IMP. In addition to the contraceptive requirements, male participants must agree not to donate sperm following discharge from quarantine until 5 effective half-lives after the last dose of IMP.
Study procedures		
Blood Sampling	Pain or bruising at the site where blood is drawn.	Blood samples will be obtained by a trained professional.
	Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle insertion.	Blood samples will be obtained by a trained professional and procedures will be put in place to avoid injury from fainting.
	There is a possibility that in the process of collecting blood a nerve may be injured.	Procedure to be performed by qualified personnel.
	Blood tests performed to address the health of the participants at screening and during the study may indicate that a participant has an infection that he/she was not previously aware of (such as human immunodeficiency virus [HIV] or hepatitis) or an unexpected illness.	The hVIVO doctor will provide the participant's general practitioner (GP), or doctor with a referral letter if the participant agrees.

Potential Risk of Clinical Significance	Description of Risk	Mitigation Strategy
Nasal sampling	Collection of respiratory (nasal) samples may cause discomfort, sneezing, watery eyes, irritated nose, or nose bleeding.	Sample collection will be performed by appropriately qualified and trained study staff.
Influenza H3N2 A/Perth/16/2009 infection from inoculation		
Influenza H3N2 A/Perth/16/2009 infection & severe complications	[redacted] Typical influenza illness: abrupt onset of rhinitis, cough, headache, chills, tiredness, nasal stuffiness, fever, malaise, myalgia (muscle aches), and sore throat. Severe complications are not expected as these tend to occur almost exclusively in infants, elderly, and persons of any age with chronic comorbidities and significant immune compromise and not in healthy adults with no comorbidities of coinfections.	The safety profile of the influenza H3N2 A/Perth/16/2009 virus is well characterised in healthy adults [redacted] Influenza infection in healthy adults usually resolves without treatment within 3 to 5 days after symptoms onset. Strict inclusion and exclusion criteria will apply to ensure only healthy adults are enrolled in this study. There will be a daily medical monitoring in a quarantine unit for at least 8 days post-HVC. Qualified medical and nursing staff in the quarantine unit will monitor for and manage any symptoms.
Transmission of influenza H3N2 A/Perth/16/2009 to participants' close contacts	Influenza H3N2 A/Perth/16/2009 presence in nasal secretions can cause infection in close contacts.	The duration of the quarantine has been designed to allow for resolution of infectious virus (culturable) before discharge. [redacted]

Potential Risk of Clinical Significance	Description of Risk	Mitigation Strategy
		As an additional precaution, participants will be instructed to avoid close contact with vulnerable individuals [redacted]
Risk of reactivation of herpes infection.	If a participant ever had a herpes infection (e.g., cold sores, genital herpes, or shingles), there is a small possibility that this infection could return after challenge.	Participants will be instructed to inform the study staff if they currently have an active herpes infection or have had one during the 30 days before enrolment. In case the participants develop any cold sore, herpes or shingles; they may be treated symptomatically while at the quarantine unit. If it continues, they will be followed up until resolved or, if necessary, dependent on medical history, will be referred to their GP or any specific department at hospital, as required.

Consult the Investigator's Brochure for detailed information on the study intervention.

2.4.1.1. Vulnerable Persons

For the purposes of possible contact after leaving the quarantine unit, the participant should avoid close contact with vulnerable individuals for 2 weeks after they leave the quarantine unit. A vulnerable individual is a person including but not limited to:

- Persons ≥65 years of age.
- Children ≤2 years of age.
- Residents of nursing homes.
- Women who are pregnant or who are trying to become pregnant.
- Persons of any age with significant chronic medical conditions such as:
    - Chronic pulmonary disease (e.g., severe asthma, chronic obstructive pulmonary disease).
    - Chronic cardiovascular disease (e.g., cardiomyopathy, congestive heart failure, cardiac surgery, ischaemic heart disease, known anatomic defects).
    - Contacts that required medical follow-up or hospitalisation during the past 5 years because of chronic metabolic disease (e.g., insulin dependent diabetes mellitus, renal dysfunction, haemoglobinopathies).
    - Immunosuppression or cancer.
    - Neurological and neurodevelopmental conditions (e.g., cerebral palsy, epilepsy, stroke, seizures).

2.4.1.2. Risk Associated with Coronavirus Disease 2019 Pandemic

hVIVO has implemented enhanced infection control measures during the pandemic to minimise risks of Coronavirus Disease 2019 (COVID-19) infection.

Risk of Increased Severity of COVID-19 Infection if Contracted After Challenge Agent Inoculation:

It has not been established that severity of COVID-19 infection could increase if contracted after inoculation with influenza H3N2 A/Perth/16/2009.

Participants will be tested for respiratory pathogens, including COVID-19, upon their arrival at the quarantine unit. They will be advised on protective measures and will need to follow infection control regimens.

Risk of Increased Severity of COVID-19 Infection After Study Intervention Administration:

There is no evidence that severity of COVID-19 infection would increase if contracted after CD388 administration.

All participants will be instructed to follow UK Government COVID-19 guidelines and will be provided with personal protective equipment while resident in the quarantine unit.

COVID-19-related emerging data will be monitored on an ongoing basis.

2.4.2. Benefit Assessment

Healthy participants will not receive direct benefit from treatment during their participation in this clinical study.

Participants may develop some immunity to influenza H3N2 A/Perth/16/2009 and benefit from a general health check at screening. Benefit may also be derived from the medical evaluations and assessments associated with study procedures. In addition, participants are contributing to the process of developing new therapies in an area of unmet medical need.

2.4.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimise risk to participants in this study, the potential risks identified in association with influenza virus infection and CD388 treatment are justified by the anticipated benefits linked to the evaluation of the antiviral activity of CD388 in the viral challenge model which will contribute to the development of a new therapy for the prevention of seasonal and pandemic influenza.

3. Objectives and Endpoints

Objectives	Endpoints
Primary:	
Efficacy	
To evaluate the prophylactic efficacy of CD388 in terms of reduction of area under the viral load-time curve (VL-AUC) after influenza viral challenge when compared to placebo.	• VL-AUC of influenza challenge virus as determined by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) on nasal samples starting a day post viral challenge (Day 1, pm) up to Day 8 (am).
Secondary:	
Efficacy	
To evaluate the effect of CD388, in reducing or shortening viral shedding after influenza viral challenge compared to placebo.	• Peak viral load of influenza as defined by the maximum viral load determined by quantifiable qRT-PCR measurements in nasal samples from Day 1 (pm) up to Day 8 (am). • Time (hours) to confirmed negative test by quantifiable qRT-PCR measurements in nasal samples from Day 1 (pm) to first confirmed undetectable assessment after peak measure.
To evaluate the effect of CD388, in reducing or shortening culturable/replicating virus after influenza viral challenge compared to placebo.	• VL-AUC of influenza challenge virus as determined by viral culture on nasal samples, from Day 1 (pm) up to Day 8 (am). • Peak viral load of influenza as defined by the maximum viral load determined by quantitative viral culture measurements in nasal samples from Day 1 (pm) up to Day 8 (am). • Time (hours) to confirmed negative test by quantifiable viral culture measurements in nasal samples from Day 1 (pm) to first confirmed undetectable assessment after peak measure.

Objectives	Endpoints
To evaluate the effect of CD388, in reducing clinical symptoms due to influenza viral challenge compared to placebo.	• Area under the curve over time of total clinical symptoms score (TSS-AUC) as measured by graded symptom scoring system collected 3 times daily from Day 1 (am) up to Day 8 (am). • Peak symptoms diary card score: peak of total clinical symptoms (TSS) as measured by graded symptom scoring system collected 3 times daily from Day 1 (am) up to Day 8 (am). • Peak daily symptom score: individual maximum daily sum of symptom score from Day 1 up to Day 8. • Time to symptom resolution as measured by graded daily symptom score system from time of peak daily symptom score to time of returning to baseline score.

To evaluate the effect of CD388, in reducing the incidence of influenza infection due to influenza viral challenge, compared to placebo.	• RT-PCR-confirmed influenza infection, defined as 2 quantifiable (≥ lower limit of quantification [LLOQ]) qRT-PCR measurements (reported on 2 or more independent samples over 2 days), from Day 1 (pm) up to Day 8 (am).
	• Occurrence of at least 1 positive quantitative (≥LLOQ) cell culture measurement in nasal samples, from Day 1 (pm) up to Day 8 (am).
	• RT-PCR-confirmed symptomatic influenza infection, defined as:
	  ○ RT-PCR-confirmed influenza infection (2 quantifiable [≥LLOQ] qRT-PCR measurements [reported on 2 or more independent samples over 2 days]), from Day 1 (pm) up to Day 8 (am), AND
	  ○ Symptoms ≥2 at a single time point.
	• RT-PCR-confirmed moderately severe symptomatic influenza infection, defined as:
	  ○ RT-PCR-confirmed influenza infection (2 quantifiable [≥LLOQ] qRT-PCR measurements [reported on 2 or more independent samples over 2 days]), from Day 1 (pm) up to Day 8 (am), AND
	  ○ Any symptoms of grade ≥2 at a single time point.

Objectives	Endpoints
	• Culture lab-confirmed symptomatic influenza infection, defined as: ○ Lab-confirmed culturable influenza infection (1 quantifiable [≥LLOQ] cell culture measurement), from Day 1 (pm) up to Day 8 (am), AND ○ Symptoms ≥2 at a single time point.
Safety	
To evaluate the safety of CD388 when compared to placebo.	• Occurrence of solicited AEs from subcutaneous dosing up to Day 0. • Occurrence of unsolicited AEs from subcutaneous dosing up to Day 28 (±3 days). • Occurrence of unsolicited AEs from subcutaneous dosing up to the final follow-up visit (Day 180 ±14 days).
Tertiary / Exploratory*:	
To further evaluate the effect of CD388, in reducing or shortening viral shedding after influenza viral challenge compared to placebo.	• Duration of quantifiable influenza qRT-PCR measurements in nasal samples from Day 1 (pm) up to Day 8 (am). Duration is defined as the time (hours) from first detectable until first confirmed undetectable assessment after their peak measure (after which no further virus is detected).
To further evaluate the effect of CD388, in reducing or shortening culturable/replicating virus after influenza viral challenge compared to placebo.	• Duration of quantitative influenza viral culture measurements in nasal samples from Day 1 (pm) up to Day 8 (am). Duration is defined as the time (hours) from first detectable until first confirmed undetectable assessment after their peak measure (after which no further virus is detected).
To further evaluate the effect of CD388, in reducing clinical symptoms due to influenza viral challenge compared to placebo.	• Time to peak as measured by graded daily symptom score system (from Day 1 [am] to the time of peak daily symptom score). • Number (%) of participants with symptom scored grade 2 or higher, from Day 1 (am) up to Day 8 (am).

Objectives	Endpoints
	• Number (%) of participants with symptom scored grade 2 or higher by time point, from Day 1 (am) up to Day 8 (am).
To further evaluate the effect of CD388, in reducing the incidence of influenza infection due to influenza viral challenge, compared to placebo.	• Number (%) of participants with lab-confirmed infection and fever (≥37.9°C). • Further sensitivity analysis may be performed on the above qRT-PCR-related incidence endpoints where detection by qRT-PCR is reported above the lower limit of detection (LLOD) instead of the LLOQ. Details will be provided in the statistical analysis plan (SAP).
To evaluate the effect of CD388, in reducing nasal discharge compared to placebo.	• Total weight of mucus produced from Day 1 (am) up to Day 8 (am). • Total number of tissues used by participants from Day 1 (am) up to Day 8 (am).
To evaluate the effect of CD388, in reducing incidence of community-acquired influenza infection compared to placebo.	• Laboratory--confirmed symptomatic influenza infection (community acquired), defined as: ○ Self-reported influenza-like symptoms, AND ○ Community acquired (not challenge virus) laboratory-confirmed influenza infection PCR measurement and/or lateral flow positive, or other equivalent) reported on any occasion from discharge from quarantine up to Day 90 and/or up to Day 180 (±14 days).
To monitor the safety of the challenge virus.	• Occurrence of unsolicited AEs from virus challenge (Day 0) up to Day 28.
To evaluate the plasma PK of CD388.	• PK parameters following CD388 administration will be determined as appropriate from the available data including: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration-time curve from time 0 to time of last quantifiable sample (AUC_{0-t}), and area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$).
To explore CD388 concentrations in nasopharyngeal swab samples.	• CD388 concentrations in nasopharyngeal swabs.

Objectives	Endpoints
To explore PK/PD of CD388.	• Plasma concentration at specific time points, or PK parameters across dose groups, will be compared to viral or symptomatic endpoints in an effort to characterise the exposure response of CD388, and will be reported separately.
To explore cytokines and chemokines in nasal samples.	• Cytokine/chemokine levels may be explored in nasal samples, related to CD388 and infection.
To explore cytokines and chemokines in serum samples.	• Cytokine/chemokine levels may be explored in serum samples, related to CD388 and infection.
To explore markers associated with the effect of CD388 or with infection.	• Gene expression (messenger RNA [mRNA]) in whole blood.
To explore viral resistance markers in influenza viral positive nasal samples	• Viral resistance markers relevant for CD388.

*Note that tertiary objectives and endpoints are optional and might be assessed only if needed; therefore, not all testing might be performed and reported.

4. Study Design

4.1. Overall Design

This is a single-centre, randomised, double-blind, placebo-controlled, proof-of-concept study in healthy adult male and female participants 18 to 55 years of age, inclusive, utilising:

- IMP (active): a single subcutaneous dose of CD388 liquid for injection
- IMP (placebo): a single subcutaneous dose of sterile normal saline for injection
- Challenge agent: influenza H3N2 A/Perth/16/2009 challenge strain, ~$10^{5.5}$ tissue culture infective dose (50%) ($TCID_{50}$), intranasally administered

The primary goal of this Phase 2a study is to assess the prophylactic antiviral activity against influenza, safety, tolerability, and PK of CD388 via a HVC model, and to explore the impact of dose levels on efficacy. Each participant will receive a single administration of CD388 or placebo; multiple dose levels of CD388 may be evaluated.

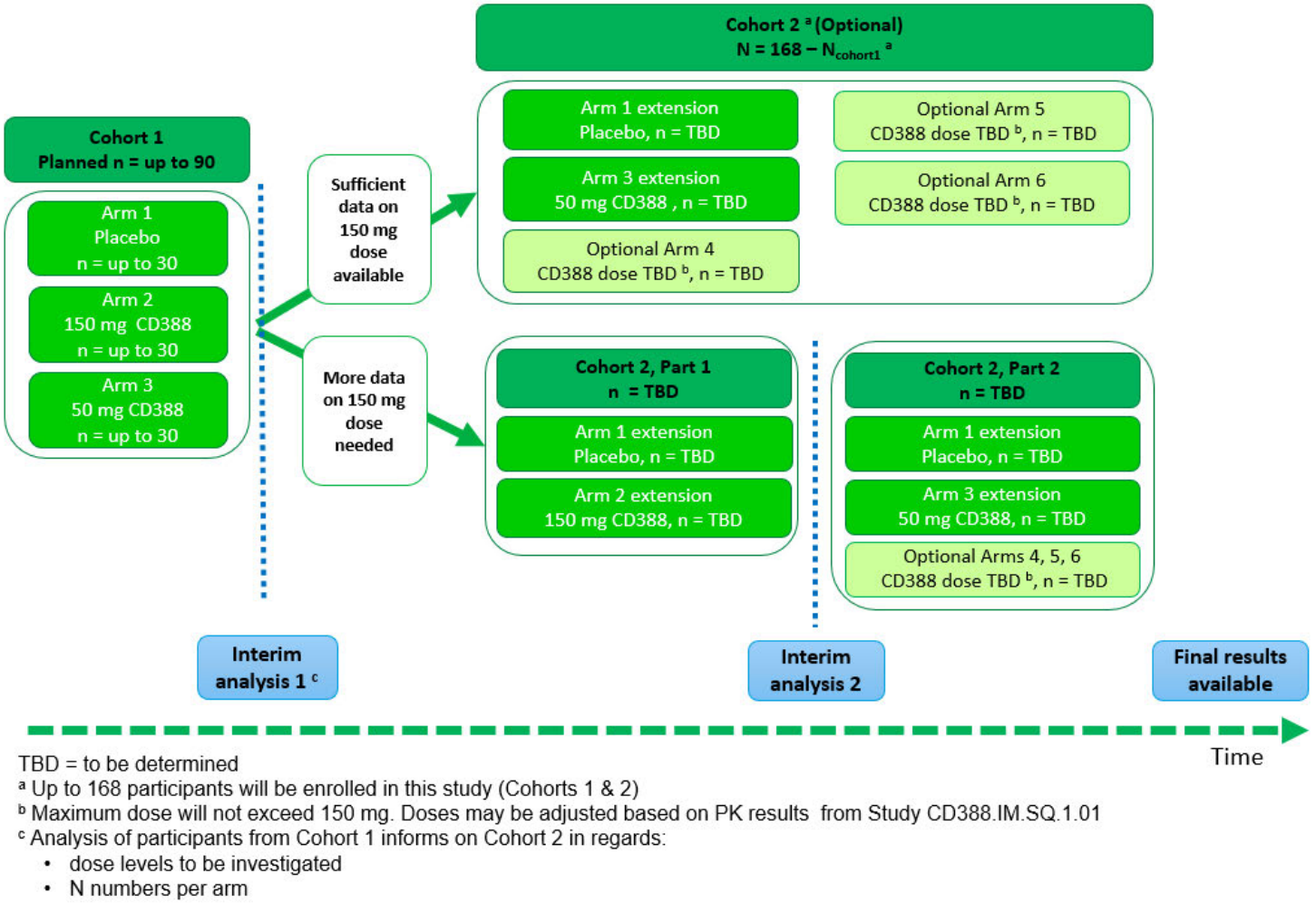
An overview of study design is provided in Figure 4-1.

A total of up to 168 participants is planned to be enrolled in this study in up to 2 cohorts. Cohort 1 will consist of up to 90 participants that will be enrolled simultaneously; a placebo arm (Arm 1, n= up to 30) and two CD388 dose arms (Arm 2 [150 mg CD388, n= up to 30] and Arm 3 [50 mg CD388, n= up to 30]). Cohort 2 details will be confirmed further to interim analysis as described below. Cohort 2 may include extension of the arms in Cohort 1 or include additional dose levels not exceeding 150 mg.

A first interim analysis will be performed for participants in Cohort 1 who have completed the inpatient phase at the time the interim analysis is performed. An optional second interim analysis may be performed within Cohort 2 depending on the outcome of the first interim analysis. Each interim analysis will inform on:

- The final participant numbers per study arm.
- The CD388 dose levels to be studied (Section 6.6, Dose Modification).
- The number of CD388 dose levels to be studied.

Participants will receive CD388 or placebo prior to being inoculated with the influenza challenge virus and will undergo assessments as per SoE. The timing of administration of CD388 or placebo is chosen so as to approximate T_{max} of CD388 in plasma at the time of challenge virus inoculation.



TBD = to be determined
[a] Up to 168 participants will be enrolled in this study (Cohorts 1 & 2)
[b] Maximum dose will not exceed 150 mg. Doses may be adjusted based on PK results from Study CD388.IM.SQ.1.01
[c] Analysis of participants from Cohort 1 informs on Cohort 2 in regards:
- dose levels to be investigated
- N numbers per arm

Figure 4-1: Overview of Study Design

The expected duration of study participation for a participant is approximately 9 months, with the following sequence and duration of study phases:

- **Screening Phase**: from Day -96 to Day -7/-6 quarantine admission. Historical generic screening data collected through the hVIVO generic screening process may be transferred to this study after the study-specific consent form has been signed by the participant.
- **Inpatient Phase**: Participants will be resident in the quarantine unit for approximately 16 days (from Day -7/-6 to Day 8). Procedures will include:
    - **Pre-HVC:**
        - Admission to quarantine unit on Day -7/-6.
        - Baseline assessments and randomisation will be conducted as per SoE up to Day -5, pre-dose.
        - Administration of CD388 or placebo on Day -5.
    - **HVC:**
        - Influenza virus inoculation on Day 0.
    - **Post-HVC:**
        - Day 1 onwards and each day – study assessments will be conducted as per SoE.
        - Participants will be discharged from the quarantine unit on Day 8 (or may remain longer at the principal investigator's [PI's] discretion).
- **Outpatient Phase:**
    - Follow-up visit(s): Day 17 (±1 day), Day 28 (±3 days), Day 60 (±7 days), and Day 120 (±14 days).
    - Final visit: Day 180 (±14 days).

The Study Schematic, showing participant progression through the study, is presented in Section 1.1, Study Schematic. The SoE is presented in Section 1.2, Schedule of Events.

4.2. Scientific Rationale for Study Design

The study will be conducted by hVIVO Services Limited, which has extensive experience with influenza challenge studies. Numerous studies have been performed using experimental influenza infection in human participants. To date, in hVIVO's studies, over 350 healthy participants have been successfully and safely inoculated with the influenza H3N2 A/Perth/16/2009 challenge strain. These studies demonstrated that healthy adults could be infected by nasal inoculation and that experimental infection was safe. This influenza strain has been shown to cause symptoms and virus shedding that closely match natural infection.

Administration of IMP and challenge with influenza H3N2 A/Perth/16/2009 will take place in hVIVO's specialised clinical facilities, either in a quarantine unit or an outpatient clinic. Standard study procedures (including collection of blood, urine, and nasopharyngeal secretions for assessment of safety and efficacy) have been employed in previous studies conducted by hVIVO.

Blinding, Control, and Randomisation

Placebo control in this study is sterile normal saline and will be used to establish the frequency and magnitude of changes in endpoints that may occur in the absence of active treatment. It will allow a comparative evaluation of the efficacy of CD388.

Blinding will prevent the occurrence of conscious and unconscious bias in the conduct and interpretation of the study.

Randomisation will be used to prevent bias in the assignment of participants to study arms, to increase the likelihood that known and unknown participant characteristics (e.g., demographic and baseline characteristics) are equally balanced across study arms, and to enhance the validity of statistical comparisons across study arms.

4.3. Justification for Dose

The dose(s) planned for this study are based on results obtained from 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), as well as the results of the ongoing first-in-human study CD388.IM.SQ.1.01. 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 at the dose of 150 mg proposed for this study dose are 32-fold in rats and 64.7-fold in monkeys using body surface area, indicating that this dose would be an acceptable highest dose from a safety perspective.

Safety results of the ongoing clinical trial CD388.IM.SQ.1.01 have indicated no significant safety findings following single subcutaneous administration of 50 and 150 mg CD388, and the study is proceeding to the maximum planned subcutaneous dose of 450 mg (see Section 2.2.2, Clinical Experience).

An inoculum titre of approximately $10^{5.5}$ tissue culture infective dose (50%) ($TCID_{50}$) of the influenza H3N2 A/Perth/16/2009 strain has been shown to cause disease profiles that are consistent with the mild to moderate disease profiles expected with wild-type challenge viruses in healthy adult participants.

4.4. Population to be Studied

Healthy participants.

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 measures for evaluation of the prophylactic antiviral activity of CD388 against influenza have been employed in previous studies conducted by hVIVO and are appropriate to characterise the efficacy of CD388, considering the CD388 mode of action.

The assessments for determining CD388 plasma concentrations are appropriate to characterise the PK profile of CD388.

Exploratory biomarkers, anti-drug antibodies (ADAs), and pharmacogenomic research are exploratory in nature and do not have predefined endpoints.

4.6. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoE or the last unscheduled visit, as applicable. If a safety visit is required after the last scheduled visit, this will be at the discretion of the PI/investigator as a duty of care, e.g., repeat spirometry or laboratory tests. These discretionary follow-up visits will not be

considered part of the study data unless they represent follow-up and closure on an AE or SAE identified during the study period.

The end of the study is defined as the date of the last follow-up (not including discretionary follow-up as mentioned above) of the last participant in the study.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

No.	hVIVO STANDARD INCLUSION CRITERIA * (Viral Challenge Volunteer Studies)
To be eligible for the study, participants must meet all the following inclusion criteria:	
1.	Written informed consent signed and dated by the participant and the PI/investigator obtained before any assessment is performed.
2.	Adult male or female aged between 18 and 55 years old, inclusive, on the day prior to signing the consent form.
3.	A total body weight ≥50 kg and body mass index (BMI) ≥18 kg/m^2 and ≤35kg/m^2.
4.	In good health with no history, or current evidence, of clinically significant medical conditions, and no clinically significant test abnormalities that that will interfere with participant safety, as defined by medical history, physical examination, (including vital signs), electrocardiogram (ECG), and routine laboratory tests as determined by the PI/investigator.
5.	Participants will have a documented medical history either prior to entering the study or following medical history review with the study physician at screening.
6.	The following criteria are applicable to female participants participating in the study. a) Females of childbearing potential must have a negative pregnancy test prior to enrolment. b) Females of non-childbearing potential: a. Postmenopausal females defined as amenorrhea for ≥12 months with no alternative medical cause. A high follicle-stimulating hormone (FSH) level, within appropriate postmenopausal range, may be used to confirm postmenopausal state in the absence of combined hormonal contraception or hormone replacement therapy. If there is <12 months of amenorrhea 2 FSH samples are required at least 4 to 6 weeks apart. b. Documented status as being surgically sterile (e.g., tubal ligation, hysterectomy, bilateral salpingectomy, and bilateral oophorectomy).

7.	The following criteria apply to female and male participants: a) Female participants of **childbearing potential** must use **1 form** of highly effective contraception. Hormonal methods must be in place from at least 2 weeks prior to the first study visit. The contraception use must continue until 5 effective half-lives (205 days) after the last dose of IMP. Highly effective contraception is as described below: a. Established use of hormonal methods of contraception described below (for a minimum of 30 days prior to the first study visit). When hormonal methods of contraception are used, male partners are required to use a condom with a spermicide: i. combined (oestrogen- and progestogen containing) hormonal contraception associated with inhibition of ovulation: 1. oral 2. intravaginal 3. transdermal ii. progestogen-only hormonal contraception associated with inhibition of ovulation: 1. oral 2. injectable 3. implantable b. Intrauterine device. c. Intrauterine hormone-releasing system. d. Bilateral tubal ligation. e. Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) where the vasectomised male is the sole partner for that woman. f. True abstinence – sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. b) Male participants must agree to the contraceptive requirements below at entry to quarantine and continuing until 5 effective half-lives (205 days) after the last dose of IMP. a. Use a condom with a spermicide to prevent pregnancy in a female partner or to prevent exposure of any partner (male or female) to the IMP.

No.	hVIVO STANDARD INCLUSION CRITERIA * (Viral Challenge Volunteer Studies)
	b. Male sterilisation with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate *(please note that the use of condom with spermicide will still be required to prevent partner exposure)*. This applies only to males participating in the study. c. In addition, for female partners of childbearing potential, that partner must use another form of contraception such as one of the highly effective methods mentioned above for female participants. d. True abstinence – sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. c) In addition to the contraceptive requirements above, male participants must agree not to donate sperm following discharge from quarantine until 5 effective half-lives (205 days) after the last dose of IMP.
8.	Sero-suitable for the challenge virus • A participant must be sero-suitable to take part in the study, i.e., he/she must have no or low pre-existing serum levels of antibodies specific to the challenge agent. Serology testing will be carried out by a haemagglutination inhibitory assay to determine serum antibody titres. As an example, a participant is considered sero-suitable if their serology (haemagglutination inhibition [HAI]) titre result is ≤10.
* Approved Final v11.0, 08FEB2022	

5.2. Exclusion Criteria

Participants are excluded from the study if any the following criteria apply:

No.	hVIVO STANDARD EXCLUSION CRITERIA (Viral Challenge Volunteer Studies)
Participants who meet any of the following exclusion criteria will not be included in the study.	
Medical History	
1.	History of, or currently active, symptoms or signs suggestive of upper respiratory tract (URT) or lower respiratory tract (LRT) infection within 4 weeks prior to the first study visit.
2.	Any history or evidence of any clinically significant or currently active cardiovascular, respiratory, dermatological, gastrointestinal, endocrinological, haematological, hepatic,

No.	hVIVO STANDARD EXCLUSION CRITERIA (Viral Challenge Volunteer Studies)
	immunological (including immunosuppression), metabolic, urological, renal, neurological, or psychiatric disease and/or other major disease that, in the opinion of the PI/investigator may interfere with a participant completing the study and necessary investigations. The following conditions apply: a) Participants with a history of resolved depression and/or anxiety 1 or more years ago can be included if the Patient Health Questionnaire (PHQ-9) and the Generalised Anxiety Disorder Questionnaire (GAD-7) is less than or equal to 4 on admission. Participants with a history of stress-related illness, which is not ongoing or requiring current therapy, with good evidence of preceding stressors may be included at the PI's discretion. As required, participants will be assessed prior to enrolment with a PHQ-9 and GAD-7 questionnaire. b) Rhinitis (including hay fever) which is clinically active or history of moderate to severe rhinitis, or history of seasonal allergic rhinitis likely to be active at the time of inclusion into the study and/or requiring regular nasal corticosteroids on an at least weekly basis, within 30 days of admission to quarantine will be excluded. Participants with a history of currently inactive rhinitis (within the last 30 days) or mild rhinitis may be included at the PI's discretion. c) Atopic dermatitis/eczema which is clinically severe and/or requiring moderate to large amounts of daily dermal corticosteroids will be excluded. Participants with mild to moderate atopic dermatitis/eczema, taking small amounts of regular dermal corticosteroids may be included at the PI's discretion. d) Any concurrent serious illness, including history of malignancy, that may interfere with a participant completing the study. Basal cell carcinoma within 5 years of initial diagnosis or with evidence of recurrence is also an exclusion. e) Participants reporting physician-diagnosed migraine can be included provided there are no associated neurological symptoms such as hemiplegia or visual loss. Cluster headache/migraine or prophylactic treatment for migraine is an exclusion. f) Participants with physician diagnosed mild irritable bowel syndrome not requiring regular treatment can be included at the discretion of the PI. g) Participants with a history of asthma where their last symptoms/treatment were in adolescence and over 6 years ago may be included at the discretion of the PI. Any participants with symptoms or treatment in adulthood would be excluded.
3.	Any participants who have smoked ≥10 pack years at any time (10 pack years is equivalent to 1 pack of 20 cigarettes a day for 10 years).

No.	hVIVO STANDARD EXCLUSION CRITERIA (Viral Challenge Volunteer Studies)
4.	Females who: a) Are breastfeeding, or b) Have been pregnant within 6 months prior to the study, or c) Have a positive pregnancy test at any point during screening or prior to dosing with IMP.
5.	Lifetime history of anaphylaxis and/or a history of severe allergic reaction or significant intolerance to any food or drug in the last 12 months, as assessed by the PI.
6.	Venous access deemed inadequate for the phlebotomy and cannulation demands of the study.
7.	a) Any significant abnormality altering the anatomy of the nose in a substantial way or nasopharynx that may interfere with the aims of the study and, in particular, any of the nasal assessments or viral challenge (historical nasal polyps can be included, but large nasal polyps causing current and significant symptoms and/or requiring regular treatments in the last month will be excluded). b) Any clinically significant history of epistaxis (large nosebleeds) within the last 3 months of the first study visit and/or history of being hospitalised due to epistaxis on any previous occasion. c) Any nasal or sinus surgery within 3 months of the first study visit.
Prior or Concomitant Medications and Assessments	
8.	a) Evidence of vaccinations within the 4 weeks prior to the planned date of dosing with IMP. b) Intention to receive any vaccination(s) before the last day of follow-up (with the exception of vaccinations recommended for COVID-19 as defined by Medicines and Healthcare products Regulatory Agency (MHRA)/government vaccination guidelines). c) No travel restrictions apply after the Day 28 [±3 days] follow-up visit; however, we expect participants to be available to attend the clinic at the Day 60, Day 120, and Day 180 follow-up visits. d) Receipt of influenza vaccine in the last 6 months prior to the planned date of viral challenge.

No.	hVIVO STANDARD EXCLUSION CRITERIA (Viral Challenge Volunteer Studies)
9.	Receipt of blood or blood products, or loss (including blood donations) of 550 mL or more of blood during the 3 months prior to the planned dosing with IMP or planned during the 3 months after the final visit.
10.	a) Receipt of any investigational drug within 3 months prior to the planned date of dosing with IMP. b) Receipt of 3 or more investigational drugs within the previous 12 months prior to the planned date of dosing with IMP. c) Prior inoculation with a virus from the same virus-family as the challenge virus. d) Prior participation in another HVC study with a respiratory virus in the preceding 3 months, taken from the date of viral challenge in the previous study to the date of expected viral challenge in this study.
11.	Use or anticipated use during the conduct of the study of concomitant medications (prescription and/or non-prescription), including vitamins or herbal and dietary supplements within the specified windows, unless in the opinion of the study physician/PI, the medication will not interfere with the study procedures or compromise participant safety. Specifically, the following are excluded: a) Herbal supplements within 7 days prior to the planned date of dosing with IMP. b) Chronically used medications, vitamins, or dietary supplements within 21 days prior to the planned date of dosing with IMP. c) Over-the-counter medications (e.g., paracetamol or ibuprofen) where the dose taken over the preceding 7 days prior to the planned date dosing with IMP has exceeded the maximum permissible 24-hour dose (e.g., ≥4 grams paracetamol over the preceding week). d) Systemic antiviral administration within 4 weeks of the planned date of dosing with IMP.
12.	a) Confirmed positive test for drugs of misuse and cotinine on first study visit. One repeat test is allowed at PI discretion. b) Recent history or presence of alcohol addiction, or excessive use of alcohol (weekly intake in excess of 28 units alcohol; 1 unit being a half glass of beer, a small glass of wine, or a measure of spirits), or excessive consumption of xanthine-containing substances (e.g., daily intake in excess of 5 cups of caffeinated drinks, e.g., coffee, tea, cola).
13.	A forced expiratory volume in 1 second (FEV_1) <80%.

No.	hVIVO STANDARD EXCLUSION CRITERIA (Viral Challenge Volunteer Studies)
14.	Positive HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV) test (HIV positive – via 3 confirmatory tests – Vidas, Genenius, and Determine, HBV confirmed via HbsAG, anti-HBs, and anti-HBc [IgG/IgM], and HCV confirmed via hepatitis C viral load).
15.	Presence of fever, defined as participant presenting with a temperature reading of ≥37.9°C on Day -7/-6 and/or pre-dose on Day -5.
Other	
16.	Those employed or immediate relatives of those employed at hVIVO or the sponsor.
17.	Any other finding that, in the opinion of the PI/investigator, deems the participant unsuitable for the study.
* Approved Final v11.0, 08FEB2022	

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

[redacted]

5.3.2. Caffeine, Alcohol, and Tobacco

[redacted]

5.3.3. Activity

[redacted]

5.4. Screen Failures

[redacted]

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Study interventions administered to participants are described in Table 6-1.

6.1. Study Intervention(s) Administered

Table 6-1: Study Interventions

Intervention Name	**CD388**	**Placebo**	**Influenza H3N2 A/Perth/16/2009 Virus**
Type	Drug	Other	Virus
Dose Formulation	Liquid for injection	Sterile normal saline for injection	Capped vial, Liquid
Unit Dose Strength(s)	100 mg/mL	-	The challenge agent titre is determined in an infectivity assay. The dose is approximately $10^{5.5}$ $TCID_{50}$
Dosage Level(s)	Arm 2: 150 mg single dose Arm 3: 50 mg single dose Cohort 2: dose lower than 150 mg, TBD	Arm 1: Single dose	A single dose of challenge agent will be delivered.
Route of Administration	Subcutaneous injection	Subcutaneous injection	Intranasal
Use	Experimental	Placebo	Infectious challenge agent
Sourcing	Provided by Cidara	Provided by Cidara or designee	Provided centrally by hVIVO
Packaging and Labelling	The details of the packaging and labelling will be provided in the study specific pharmacy manual.	The details of the packaging and labelling will be provided in the study specific pharmacy manual.	Influenza challenge agent will be provided in vials. The details of the challenge agent provision will be provided in the analytical plan (AP).

Intervention Name	CD388	Placebo	Influenza H3N2 A/Perth/16/2009 Virus
Current/Former Name(s) or Alias(es)	Not applicable	Not applicable	Not applicable

6.2. Preparation/Handling/Storage/Administration/Accountability

6.2.1. Investigational Medicinal Product

hVIVO will receive supplies of IMP (CD388/placebo) after the supply has received qualified person sign off by the Good Manufacturing Practice (GMP) sponsor's representative/pharmacy provider and has been released for shipment. All IMP (CD388/placebo) supplies will be used only for this protocol and for no other purpose.

IMP (CD388/placebo) will be supplied at the beginning of the study. Once received at hVIVO, hVIVO study staff will perform stock level accountability and the IMP (CD388/placebo) liquid for injection will be stored securely, according to the directions on the IMP labels. IMP (CD388/placebo) accountability will be controlled by hVIVO and monitored by the study monitor throughout the study and at study close-out.

The PI/investigator will ensure that all supplies are received by a responsible person, all deliveries and returns are documented and signed for, and the condition of the IMP (CD388/placebo) is monitored. Accurate records will be kept of when and how much IMP (CD388/placebo) is dispensed and used in the study. Any reasons for departure from the protocol dispensing regimen will be recorded.

Accountability records will be available for verification by the study monitor at each monitoring visit. At the completion of the study, there will be a final reconciliation of all IMP (CD388/placebo).

A single subcutaneous dose of CD388/placebo will be given to each participant. Details on dose preparation and administration are provided in the study-specific pharmacy manual. An overview of the treatments per study arm is given below.

- Arm 1: Placebo, single subcutaneous injection
- Arm 2: 150 mg CD388, single subcutaneous injection
- Arm 3: 50 mg CD388 , single subcutaneous injection
- Arm 4 (optional): CD388 dose TBD*, single subcutaneous injection
- Arm 5 (optional): CD388 dose TBD*, single subcutaneous injection
- Arm 6 (optional): CD388 dose TBD*, single subcutaneous injection

* Maximum dose will not exceed 150 mg. Doses may be adjusted based on PK results from Study CD388.IM.SQ.1.01.

6.2.2. Challenge Agent

The challenge agent used in this study is influenza H3N2 A/Perth/16/2009.

The challenge agent stock was manufactured under current GMP (cGMP). The challenge agent stock has undergone quality testing performed during manufacturing (identity, appearance, sterility, infectivity, and contaminants) according to pre-determined specifications, and has subsequently also passed an extensive panel of adventitious agent testing. The challenge agent is stored in a secure -80ºC freezer (normal temperature range -60°C to -90°C).

Each participant will be allocated a unique vial containing the challenge agent and will receive the inoculum intranasally. The inoculum will be prepared and/or provided according to the hVIVO AP and administered in accordance with hVIVO SOPs.

All administrations will be made by a member of the study staff and witnessed by a second study staff member. The exact time of challenge agent inoculation will be recorded in the administration log. Accurate records will be kept of when and how much inoculum is prepared and used. The oversight process will be signed off prior to administration of the challenge agent. Any noncompliance or problems with the inoculation will be recorded in the participant's source notes and reported to the PI/investigator.

Following challenge agent inoculation, participants will be closely observed for 24 hours specifically for the occurrence of potential allergic reactions and any AEs. [redacted]

6.2.3. All Study Interventions

The PI/investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorised investigator site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled area, and monitored (manual or automated) in accordance with the labelled storage conditions with access limited to the PI/investigator and authorised investigator site staff.

The PI/investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records)

Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

6.3. Randomisation and Blinding

[redacted] the randomisation number encodes the participant's assignment to 1 of 3 study arms: placebo (Arm 1, n= 24 to 30), and two CD388 dose arms (150 mg CD388 [Arm 2, n=30] and 50 mg CD388, [Arm 3, n= 18 to 30]). This initial randomisation schedule, in use prior to Non-Substantial Amendment 03, used 2 varying block sizes (12 and 3) and 2 sets of randomisation ratios (4:5:3 and 1:0:2) to facilitate achieving the targeted sample sizes for the interim analysis.

Block					Cumulative			
Block	Arm 1 Placebo	Arm 2 High dose (150 mg CD388)	Arm 3 Low dose (50 mg CD388)	Block size	Arm 1 Placebo	Arm 2 High dose (150 mg CD388)	Arm 3 Low dose (50 mg CD388)	Randomised
1	4	5	3	12	4	5	3	12
2	4	5	3	12	8	10	6	24
3	4	5	3	12	12	15	9	36
4	4	5	3	12	16	20	12	48
5	4	5	3	12	20	25	15	60
6	4	5	3	12	24	30	18	72
7	1	0	2	3	25	30	20	75
8	1	0	2	3	26	30	22	78
9	1	0	2	3	27	30	24	81
10	1	0	2	3	28	30	26	84
22	1	0	2	3	29	30	28	87
23	1	0	2	3	30	30	30	90

At the time of Non-Substantial Amendment 03 , this randomisation schedule was modified to ensure achievement of the largest possible sample-sizes in arm 1 (Placebo) and arm 2 (High dose) at the time of the planned first interim analysis. Participants enrolled under Non-Substantial Amendment 03 will be randomised 1:1 to either arm 1 (Placebo) or arm 2 (150 mg CD388) until Cohort 1 enrolment is complete. Afterwards, a new randomisation schedule will be prepared, taking into account the decisions taken based on the results of the first interim analysis.

Randomisation numbers will be assigned sequentially in ascending order; and once assigned, that randomisation number shall not be reassigned. The study site will keep a log of the randomisation number assigned to each participant.

A designated unblinded statistician, separate from the conduct or analysis of the study, will be responsible for the computer-generated randomisation schedule. Sealed copies of the randomisation code will be stored in a secure location.

Randomisation numbers will follow a 4-digit format e.g., [0001]. If participants are replaced as per Section 7.4, Participant Replacement Strategy, the replacement participant will be assigned a new, unique randomisation number equalling the randomisation number of the replaced participant, plus 1000. This will ensure that the replacement participant receives the same allocated, blinded treatment as the participant who is being replaced.

A copy of the randomisation code list will be sent to the unblinded pharmacist preparing the IMP, so that CD388/placebo can be prepared for each participant as appropriate. The GMP pharmacy provider 's pharmacist/designee will prepare the participant level IMP doses in line with the randomisation schedule.

Each participant will be dispensed blinded IMP (CD388/placebo), labelled with his/her unique randomisation number, throughout the study. With the exception of the unblinded sponsor team, unblinded sponsor designated bioanalytical personnel, unblinded drug administration personnel, unblinded pharmacist, unblinded IMP management personnel at the clinical site, the unblinded statistician preparing the randomisation code list, the statisticians performing the interim analyses, and the quality assurance (QA) auditors where necessary, the PI/investigator and all other clinical and nonclinical staff, (including data management staff), and the participants will remain blinded to the treatment allocation until after the database has been locked and approval for study unblinding has been given.

For the interim analysis, adequate firewalls will be setup to ensure that the clinical and nonclinical staff are kept blinded to treatment allocation and interim results. Details will be provided in the SAP.

Once the interim analysis has been performed and Cohort 1 has completed the inpatient phase, new participants will continue to be randomized between the chosen arms for Cohort 2 using a suitable randomization schedule consistent with the planned number and size of the study arms. The measures described above to protect the blind will stay in place until the final unblinding.

Following database lock, on receipt of authorisation from the sponsor, a copy of the randomisation code list will be provided to the study statistician to conduct study unblinding prior to analysis.

Individual access to a secured Interactive Web Response System (IWRS) will be provided to the investigator. The website, compliant with 21CFR part 11 guidelines, will be used if unblinding is necessary. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. The blind should only be broken where knowledge of the IMP received is required to provide appropriate patient care.

Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant.

When the investigator breaks the code, he/she will have to indicate on the web site the reason for unblinding. The person who performed the unblinding and the date of time of code breaking will be automatically recorded. After confirmation the nature of treatment will appear on the screen. A notification with the nature of treatment will also be provided by email. A notification, without the nature of treatment, will be provided to the study team. The investigator must notify the sponsor within 24 hours that the code has been broken. Even if the code is broken, blood samples for safety, efficacy, PK, and other assessments will continue to be drawn for the remainder of the planned study period following the last dose if doing so will not compromise participant welfare.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention and challenge agent directly from the PI/investigator or designee, under medical supervision. The date and time of each dose administered at the study site will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the PI/investigator site staff other than the person administering the study intervention.

Any noncompliance or problems with the administration of the study intervention will be recorded in the participant's source notes and reported to the sponsor, if appropriate.

6.5. Concomitant Therapy

Any medications taken and changes in medications will be recorded in the source data from the time of the participant signing the study -specific ICF up to the final follow-up visit performed on Day 180 (±14 days). Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the quarantine/outpatient stage will be stored, prescribed, and administered in line with their label-specific requirements, and recorded according to the parameters required by the clinical database.

Participants will be reminded to refrain from using any over-the-counter medication without the approval of the PI/investigator and must notify the study staff as soon as possible if they are prescribed any medication. All medications must be stopped prior to the planned date of dosing with IMP, unless in the opinion of the PI/investigator and/or sponsor's medical expert (SME) the medication will not interfere with the study procedures or compromise participant safety.

Medications prohibited throughout the study are shown in Table 6-2.

Table 6-2: Prohibited Medication (Healthy Participants)

Prohibited medication	Washout
Systemic (oral and parenteral) antiviral drugs.	[redacted]
Use or anticipated use during conduct of the study of concomitant medications (prescription and non-prescription), including vitamins or herbal and dietary supplements, unless in the opinion of the PI/investigator the medication will not interfere with the study procedures or compromise participant safety.	[redacted]

Prohibited medication	Washout
Any IMP used in another study.	[redacted]

Any concomitant medication required for the participant's welfare may be given by the PI/investigator. However, it is the responsibility of the PI/investigator to ensure that details regarding the medication and the reason for its use are recorded appropriately in the source notes to permit their transfer to the clinical database.

[redacted]

Medications which are permitted throughout the study are shown in Table 6-3.

Table 6-3: Permitted Medication

Permitted medication	Time period
Paracetamol	[redacted]
Ibuprofen	[redacted]
Hormonal contraceptives	Allowed at any time during the study.
Prescription and non-prescription medications, including vitamins or herbal and dietary supplements, not listed in prohibited medications are subject to approval by the PI/investigator. If, e.g., in an outbreak or pandemic, a newly instated national vaccination programme is applicable to an individual participant, the PI/investigator and sponsor will discuss on an individual basis if concomitant vaccination may be allowed, study dosing/viral challenge postponed, or the participant withdrawn from the study.	

6.6. Dose Modification

In this study, a single dose of either CD388 or placebo is to be administered to enrolled participants. The CD388 dose to be administered in Arm 2 and Arm 3 have been defined (i.e., 150 mg and 50 mg, respectively). The CD388 doses in any additional study arms in Cohort 2 will be determined based on PK results obtained in the first-in-human study CD388.IM.SQ.1.01, as well as the interim analyses. However, the maximum dose will not exceed 150 mg.

6.7. Treatment of Overdose

For this study, any dose of any drug administered as part of the study greater than the dose prescribed by the protocol will be considered an overdose.

In the event of an overdose, the PI/investigator should:

1. Contact the SME/medical monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities possibly associated with overdose and the participant will be clinically followed up until any AE/SAE has resolved.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

The sponsor and/or sponsor delegate is responsible for notifying the MHRA and Research Ethics Committee (REC) of the serious breach within 7 days of becoming aware of it.

7. Discontinuation of Study Intervention/Withdrawal

7.1. Participant Withdrawal

A participant may withdraw their consent to participate in the study at any time, for any reason, without prejudice to his/her future medical care. Participants may decline to give a reason for their withdrawal. Additionally, the PI/investigator may withdraw a participant if, in their clinical judgement, it is in the best interest of the participant or if the participant cannot comply with the protocol. Wherever possible, the tests and evaluations listed for the early withdrawal visit should be carried out, and if clinically indicated, the participant should be invited back for a final follow-up visit.

Sponsor representatives (both SME/medical monitor and clinical operations) should be notified of all study withdrawals in a timely manner, and in cases where the withdrawal is due to a medical reason the participant would be referred to his/her GP.

[redacted]

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the PI/investigator must document this in the site study records.

7.2. Participant Discontinuation

Participants will be withdrawn from study intervention for any of the reasons listed below. These participants must not receive any additional study intervention but should continue to be followed for safety. Additional unscheduled visits may be performed for safety reasons.

- Noncompliance with the study requirements and restrictions.
- Clinically significant abnormal laboratory findings, which in the opinion of the PI/investigator and/or sponsor precludes further participation in the study.
- Development of intercurrent illness, which in the opinion of the PI/investigator would compromise the health of the participant or the study objectives.
- The PI/investigator's decision that withdrawal from further participation would be in the participant's best interest.
- Termination of the study at the discretion of the PI/investigator or sponsor for safety, behavioural, or administrative reasons.
- The wish of the participant.
- Any intervention-related SAEs.
- Anaphylactic reaction following dosing.
- The participant becomes pregnant.

Participants who are withdrawn from the study, will be requested to attend an early withdrawal visit, with assessments as detailed in the SoE.

7.2.1. Temporary Discontinuation/Temporary Delay in Enrolment

[redacted]

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the PI/investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a follow-up letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1, Regulatory, Ethical, and Study Oversight Considerations.

7.4. Participant Replacement Strategy

Participants may be replaced in this study.

[redacted]

7.5. Stopping Rules

The PI/investigator and the SME will perform safety reviews on available clinical and virology data as appropriate during the quarantine period.

Four clinical scenarios relating to the incidence of SAEs/suspected unsuspected serious adverse reactions (SUSARs) during the study and the procedures that should be performed in each case are presented in Table 7-1.

Table 7-1: Study Stopping Rules

Status	Criterion	Procedure
1	A serious adverse reaction has been reported (i.e. a serious adverse event considered at least possibly related to the IMP administration) in one subject.	If such a status occurs at any point during the study, then further administration of the IMP in new participants will not take place. The PI/investigator and the SME will review the data and decide on whether it is appropriate to recommence IMP dosing in new participants (approval of a substantial amendment from the Competent Authorities is required) or terminate the study.
2	Severe non-serious adverse reactions (i.e. severe non-serious adverse events considered as, at least, possibly related to the IMP administration) in two subjects in the same cohort, independent of within or not within the same system-organ-class)	If such a status occurs at any point during the study, then further administration of the IMP in new participants will not take place. The PI/investigator and the SME will review the data and decide on whether it is appropriate to recommence IMP dosing in new participants (approval of a substantial amendment from the Competent Authorities is required) or terminate the study.
3	No SUSAR(s) have been reported but an overall pattern of clinical changes or symptoms exists, attributed to the IMP, which may appear minor or moderate in terms of individual AEs or SAEs severity, but which collectively are determined to suggest a risk for further participant involvement.	If such a status occurs at any point during the study, then further administration of IMP in new participants will not take place. The PI/investigator and the SME will review the data and decide on whether it is appropriate to recommence IMP dosing in new participants (approval of a substantial amendment from the Competent Authorities is required) or terminate the study.
4	Unexpected virus-related SAE(s) or unexpected virus-related AE(s) of clinical concern have been reported following viral challenge.	If such a status occurs at any point during the study, then the PI/investigator and the SME will review the data and decide based on expectedness* of the viral event. If the event is unexpected, further administration of the virus will not take place. The PI/investigator and the SME will review the data and decide on whether it is appropriate to recommence inoculation (approval of a substantial amendment from the Competent Authorities is required) or terminate the study.

* Expectedness will be assessed by referring to the challenge virus dossier.

A final follow-up visit will be performed on Day 180 (±14 days). Follow-up of any event should continue until resolution (return to normal or baseline values), stabilisation, or the participant is lost to follow-up.

Further enrolment into the study may be either temporarily or permanently discontinued if:

- An unacceptable number of severe or life-threatening exacerbations of AEs take place (as determined by the PI/investigator).
- Any clinically significant life-threatening AEs considered related to the study intervention as determined by the PI/investigator occur.

7.6. Adaptive Features

This study is designed to be able to utilise adaptive features to enhance study safety, efficiency, and efficacy. These design elements are predefined in their scope and limit, as detailed in Table 7-2.

The implementation of study-specific adaptive features will be documented in an amendment. Generic adaptive features may be implemented at any time at the discretion of the PI/investigator.

Table 7-2: Adaptive Features

Adaptive Design Category	Feature	Limit
Generic		
Cohort(s)	1. Participants who have been withdrawn (for any reason) may be replaced (sponsor and/or PI discretion). 2. Participants who are replacing a withdrawn participant may be randomised for inclusion, and dosed/challenged: a. In an ongoing cohort b. In a new cohort c. Separately 3. The number of participants enrolled in each cohort may be reduced or increased (sponsor and/or PI discretion) to best meet the study objectives.	1. The stopping rules of the study must be always adhered to, and replacement participants may not be enrolled to replace participants who have been withdrawn from the study due to any reason related to safety. 2. The total number of study participants will not exceed 168. 3. Replacement participants will be given replacement randomisation numbers (see Section 7.4, Participant Replacement Strategy). 4. All protocol-defined rules and safety criteria must be met before any study part, cohort, or participant commences the study.
Sample/specimen	1. The PI/investigator may perform additional safety assessments, at any time, if they believe them to be clinically required.	1. The maximum blood volume will not be exceeded. 2. Any required additional safety assessments, or specialist referrals, will be conducted on a

Adaptive Design Category	Feature	Limit
	2. Where clinically required (sponsor and/or PI discretion), participants may be referred for consultation(s) and/or investigation(s) under the care of a specialist physician.	case-by-case basis. As such the maximum number needed cannot be prospectively defined.
Duration of inpatient stay	1. A participant's inpatient stay may be prolonged if discharge criteria of minimal infectiousness is not met (sponsor and/or PI discretion).	1. Must meet the terms and criteria as detailed in the participant information sheet. 2. Participants must always be able to leave the study site unhindered if they wish to do so. 3. The additional stay is triggered based on the minimal infectiousness discharge criteria not being met (see Section 8.2.2.2, Influenza Discharge Test/Rapid Viral Antigen Test), and the participant's suitability for residential stay will be assessed on a case-by-case basis. As such, a maximum length of stay cannot be prospectively defined.
Study-specific		
Dose level and cohort size	1. The CD388 dose levels in Cohort 2 are TBD based on the PK results from Study CD388.IM.SQ.1.01, but will not exceed 150 mg. The interim analysis results from Cohort 1 will also inform the CD388 dose level selection and sample size in each study arm of Cohort 2.	1. The dose will not exceed 150 mg.

8. Study Assessments and Procedures

Unless otherwise stated, study assessments will be performed according to hVIVO SOPs.

Study procedures and their timing are summarised in the SoE (Section 1.2, Schedule of Events). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoE, is essential and required for study conduct. Immediate safety concerns should be discussed with the sponsor upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The PI/investigator will maintain a screening log to record details of all participants screened and to document eligibility or record the reasons for screening failure, as applicable.

For all study assessments, the pre-dose value obtained nearest to dosing will be used as the baseline measure for assessments, unless stated otherwise.

[redacted]

Where applicable, unless otherwise stated, laboratory normal ranges will be documented and saved in the PI/investigator trial master file.

8.1. Demographics and Baseline Characteristics

8.1.1. Demographics

Demographic data will be recorded at the screening visit.

8.1.2. Height, Body Weight, and Body Mass Index

Height and body weight measurements will be recorded in compliance with hVIVO's standard procedures.

Body mass index will be calculated as: $\text{BMI } (kg/m^2) = \frac{\text{Body Weight (kg)}}{\text{Height } (m)^2}$

8.1.3. Medical and Medication History

Medical and medication histories will be recorded at screening, including, but not limited to, detailed histories on current contraception, and allergies (e.g., rhinitis, dermatitis, food, aspirin/non-steroidal anti-inflammatory drugs and asthma).

8.1.4. Challenge Agent Serology Samples

A participant must be sero-suitable to take part in the study, i.e., he/she must have no or low pre-existing serum levels of antibodies specific to the challenge agent. This antibody titre cut-off for serosuitability will be described in the applicable hVIVO policy.

Serum levels of pre-existing influenza-specific antibodies will be determined using a haemagglutination inhibitory assay, as described in the AP.

8.1.5. Patient Health Questionnaire and Generalised Anxiety Disorder Questionnaire

Patient Health Questionnaire-9 and GAD-7 questionnaires will be used at the discretion of the PI/investigator to assess participants' eligibility in terms of ability to tolerate isolation in the quarantine unit.

8.2. Respiratory Samples

The following exploratory nasal and throat (as required) sampling procedures will be performed during the study and are detailed in the sections below:

- Nasosorption (nasal wick)
- Nasopharyngeal swab

Where any nasal sampling time points occur together the order of sampling will typically be (1) nasosorption (2) nasopharyngeal swab.

8.2.1. Nasosorption

A nasosorption (Class 1 Device) procedure will be used to collect samples of epithelial lining fluid for:

- Inflammatory markers.
- Other protein biomarkers e.g., antibodies.

Remaining epithelial lining fluid may be stored and used for exploratory purposes.

8.2.2. Nasopharyngeal Swab

Nasopharyngeal swabs will be performed to collect samples of nasal material for:

- Respiratory pathogen screen
- Influenza discharge test
- Viral shedding/load assessments (see Section 8.3.1)
- Exploratory purposes (see Section 8.3.5).

Remaining material from the nasopharyngeal swabs may be stored and used for exploratory purposes.

8.2.2.1. Respiratory Pathogen Screen

On entry to quarantine, a nasopharyngeal swab will be collected and tested to detect the presence of a set of respiratory pathogens that could potentially contraindicate a person's participation in the study. The methodology to be used to conduct the respiratory pathogen screen will be documented in the AP.

[redacted]

Any additional screening tests will be conducted at the discretion of the PI/investigator.

8.2.2.2. Influenza Discharge Test/Rapid Viral Antigen Test

Where required, a rapid viral antigen test will be used to determine the presence of influenza in a nasopharyngeal swab sample taken prior to discharge from the quarantine unit on Day 8. A Biofire test may be used as an alternative test for this purpose, details of which will be documented in the AP. A rapid viral antigen test/Biofire test will be performed at the discretion of the PI/investigator and only if indicated for a clinical or other reason.

8.2.3. Viral Sequencing

[redacted]

8.3. Efficacy Assessments

8.3.1. Viral Shedding Assessment

Viral titre will be determined by quantitative reverse transcription polymerase chain reaction (qRT-PCR) and/or a viral culture assay to investigate the following parameters:

- Viral load
- Infectivity status and rate
- Viral dynamics (e.g., duration, peak, time to resolution).

8.3.2. Participant Diary Cards

Symptom Diary Card

Participants will report and assess the severity of any challenge agent-related signs and symptoms 3 times per day during quarantine, at the same time each day (±1 hour), using the hVIVO symptom diary card. This information will be collected using a paper form.

The following symptoms in the 13-item symptom questionnaire will be graded on a scale of 0-3 (grade 0: no symptoms; grade 1: just noticeable; grade 2: clearly bothersome from time to time but does not interfere with me doing my normal daily activities; grade 3: quite bothersome most or all of the time, and it stops me participating in activities); shortness of breath and wheeze have an additional grade, i.e., grade 4: symptoms at rest.

- Runny nose
- Stuffy nose
- Sneezing

- Sore throat
- Earache
- Malaise/tiredness
- Headache
- Muscle and/or joint ache
- Chilliness/feverishness
- Cough
- Chest tightness
- Shortness of breath
- Wheeze

Additional to the categorical symptom diary card, a visual analogue scale diary card using a 100 mm scale, with the same symptoms, will be completed by the participants.

8.3.3. Nasal Discharge Collection from Paper Tissues

Each participant will be given pre-weighed packets of paper tissues. Participants will be asked to place single tissues used for nose blowing or sneezing into a specified collection bag (for that participant only).

A daily 24-hour paper tissue collection will take place throughout the quarantine period. Distribution of paper tissues and collection bags will start on Day -1, with the first collection on Day 0. Thereafter, distribution and collection of tissues will occur daily at the same time each day in the morning until discharge from quarantine.

24-hour paper tissue collections will be analysed to determine the following over the quarantine period:

- 24-hour nasal discharge weight
- The number of paper tissues used for nose blowing or sneezing over each 24-hour period

8.3.4. Respiratory Tract Infection Surveillance

[redacted]

8.3.4.1. Active Surveillance

[redacted]

[redacted]

8.3.4.2. Passive Surveillance

[redacted]

8.3.4.3. Assessment for Potential Influenza Respiratory Tract Infection

[redacted]

- [redacted]
- [redacted]
- [redacted]
  - [redacted]

[redacted]

- [redacted]

[redacted]

8.3.5. Exploratory Assessments

Plasma concentrations of CD388 or PK parameters across dose groups may be compared to viral and/or symptomatic endpoints to characterise the PK/PD relationship. In addition, CD388 concentrations in nasopharyngeal swabs may be explored.

Nasal samples and/or blood cytokine and chemokine proteomic profile and/or mRNA profile may be assessed for associations with CD388 response, and other endpoints.

Further details will be described in the SAP.

8.4. Safety Assessments

8.4.1. Complete Physical Examination

A complete physical examination to include a full systemic assessment.

8.4.2. Symptom-directed Physical Examination

Symptom-directed physical examinations will be conducted on Days -5, 2, 3, 4, 180, and as deemed appropriate by the PI/investigator and may include (as applicable) examination of the eyes, ears, nose, throat, and respiratory system/chest (via stethoscope). Based upon the presence or absence of clinical signs and symptoms, PI/investigator discretion will be used to determine the requirement to perform certain ongoing assessments.

[redacted]

8.4.3. Reactogenicity Events (Diary Card)

Participants will be provided with the reactogenicity diary card to complete, once daily on Day -5 to Day -1.

[redacted]

- [redacted]

[redacted]

If there are any events ongoing after the diary reporting period, these events will be followed until resolution and the stop date recorded.

8.4.3.1. Grading Scale

The grading scale used to assess the local reactions of injectable products as reported in the reactogenicity diary has been adopted from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventative vaccine clinical trials. [redacted]

Local Reaction Grading Scale:

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

a. [redacted]

b. [redacted]

8.4.4. Vital Signs and Tympanic Temperature

Vital signs assessments will be recorded as follows:

- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

Study-specific normal ranges for vital signs and tympanic temperature are provided in Appendix 4, Normal Ranges.

If a result is out of the normal range and meets the criteria for an AE, the severity of the AE will be guided by sponsor requirements using the Division of AIDS (DAIDS) table (July 2017).

[redacted]

8.4.5. Electrocardiogram

Study-specific normal ranges are provided in Appendix 4, Normal Ranges.

[redacted]

8.4.6. Clinical Safety Laboratory Assessments

8.4.6.1. Urinalysis

Clinical urine safety analysis will be undertaken using commercially available urine test strips (i.e., dipsticks) that provide an instant result, which will be documented in the source data.

Urinalysis will be performed to evaluate the parameters described in Appendix 2, Clinical Laboratory Tests.

[redacted]

8.4.6.2. Drugs of Misuse and Cotinine

[redacted]

8.4.6.3. Alcohol Breath Testing

[redacted]

8.4.6.4. Safety Blood Analysis and Assessments

Appendix 2, Clinical Laboratory Tests, describes the safety blood tests that will be performed including, but not limited to, haematology, biochemistry, coagulation, serology (HIV, hepatitis), thyroid function test, and cardiac enzymes. Additional safety assessments will be conducted at the discretion of the PI/investigator, as required.

8.4.7. Pregnancy Tests and Follicle-stimulating Hormone

Female participants of childbearing potential are to have a urine pregnancy test at screening. Participants will only be enrolled if the pregnancy test is negative.

[redacted]

8.4.8. Lung Function

Spirometry

Spirometry will be performed according to hVIVO SOPs. Height at screening will be used as the baseline measurement for all spirometry assessments.

[redacted]

[redacted]

8.5. Recording of Adverse Events/Serious Adverse Events

The PI/investigator is responsible for ensuring that all AEs/SAEs and pregnancies are identified, evaluated, recorded, and reported in a timely manner as per regulatory requirements, hVIVO SOPs, and the study-specific protocol. The PI/investigator is also responsible for ensuring that the medical management (including follow-up) of AEs/SAEs and, where appropriate, pregnancy symptoms/complications is provided by competent investigator site staff.

The sponsor of the study will also perform an evaluation of seriousness, causality, and expectedness of all SAEs.

The definitions of an AE/SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE/SAE, and other reportable safety event reports can be found in Appendix 3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.5.1. Time Period and Frequency for Collecting Adverse Events and Serious Adverse Event Information

All AEs/SAEs will be collected from signing of the study-specific ICF until the last scheduled follow-up visit at the time points specified in the SoE.

Investigators are not obligated to actively seek AEs/SAEs after conclusion of study participation. However, if the PI/investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the PI/investigator must promptly notify the sponsor.

8.5.2. Method of Detecting Adverse Events/Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs/SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Care will be taken not to introduce bias when detecting AEs/SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.5.3. Follow-up of Adverse Events/Serious Adverse Events

After the initial AE/SAE report, the PI/investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs will be followed until resolution (return to normal or baseline values), stabilisation, or the participant is lost to follow-up (as defined in Section 7.3, Lost to Follow-up). Further information on follow-up procedures is provided in Appendix 3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.5.4. Regulatory Reporting Requirements for Serious Adverse Events

Any SAE will be reported immediately by the PI/investigator to the sponsor (in practice reporting within 24 hours of the PI/investigator's knowledge of the event). This is essential so that the sponsor can meet its reporting obligations for the study. Immediate reports may be verbal (a written record of this verbal notification will be retained) or in writing. Immediate reports must be followed up promptly by detailed, written reports.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators, as necessary.

A PI/investigator who receives an investigator safety report (e.g., CIOMS) describing an SAE or other specific safety information (e.g., SAE/SUSAR) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the REC, if appropriate according to local requirements.

Further information on regulatory reporting requirements is provided in Appendix 3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.5.5. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected from signing of the study-specific ICF onwards until the last study assessment as outlined in the SoE. If a pregnancy is reported, the PI/investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

[redacted]

8.6. Pharmacokinetics

Blood samples will be collected for measurement of CD388 concentrations as specified in the SoE.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of CD388. Samples collected for analyses of CD388 blood concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during

or after the study. Genetic analyses will not be performed on these blood samples. Participant confidentiality will be maintained.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded study staff until the study has been unblinded.

8.6.1. Pharmacokinetic Blood Samples

Blood samples for the evaluation of PK parameters of CD388 will be collected according to the SoE, and processed and sent to the sponsor's PK vendor according to the AP.

[redacted]

[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
* [redacted]	

8.6.2. Pharmacokinetic Nasopharyngeal Swab Samples

Nasopharyngeal swabs for the evaluation of PK parameters of CD388 will be according to the SoE, and processed and sent to the sponsor's PK vendor according to the AP.

8.6.3. Pharmacokinetic Parameters

Pharmacokinetic parameters of interest may include:

AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{½}$

Pharmacokinetic parameters will be calculated using non-compartmental methods based on the actual elapsed time post-dose. Plasma concentrations at nominal times and PK parameters will be summarised descriptively.

8.6.4. Anti-drug Antibodies

Serum samples will be collected to measure the incidence of ADAs to CD388 during the study.

8.7. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8. Immunology Assessments

[redacted]

8.9. Genetics

[redacted]

8.10. Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoE:

- Nasosorption
- Nasopharyngeal swab
- Serum

[redacted]

8.10.1. Immunology Biomarker Evaluations

Nasal samples and blood may be used for exploratory immunology and genomic analysis related to viral infection/study intervention(s), including but not limited to:

- Influenza antibodies
- T cells
- RNA transcriptomics
- DNA
- Immunoglobulin A antibodies

Sample processing, storage, and assessments will be detailed in the AP.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary statistical hypothesis is that prophylactic treatment with CD388 at the dose of 150 mg will significantly reduce influenza VL-AUC as determined by qRT-PCR on nasal samples compared to placebo.

9.2. Sample Size Determination

A total sample size of 168 participants is estimated to be sufficient to achieve the objectives of this study.

Depending on recruitment, the number enrolled at the planned first interim analysis is expected to be up to 30 participants in Arm 1 (placebo), Arm 2 (150 mg CD388), and Arm 3 (50 mg CD388). An example of sample size estimates for the interim analysis depending on the recruited number of subjects is shown below:

- The sample size of 30 participants per arm will have 95% power to detect a statistically significant difference between groups, using a Wilcoxon rank-sum test with a one-sided type-1 error rate of 0.025, assuming that the probability that the VL-AUC for a participant in Arm 2 (150 mg CD388) is less than the VL-AUC for a participant in Arm 1 (placebo) is 0.75.
- The sample size calculations used the method proposed in Shieh et al, 2009.

Probability ($AUC_{CD388} < AUC_{Placebo}$)	**0.60**	**0.65**	**0.70**	**0.75**	**0.80**
Power at Interim analysis					
Interim analysis Arm 1 n=30 vs Arm 2 n=30	0.259	0.515	0.785	0.951	0.996

9.3. Participant Sets for Analyses

The participant sets for analysis are defined in Table 9-1.

Table 9-1: Study Participant Sets for Analysis

Participant Analysis Set	Description
Enrolled	All participants who sign the study-specific ICF.
Intent-to-treat (ITT) analysis set	All participants randomly assigned to study intervention.
Intent-to-treat infected (ITT-I) analysis set	All participants randomly assigned to study intervention and infected with challenge agent as per the definition of laboratory-confirmed infection for this protocol, i.e., qRT-PCR-confirmed influenza infection, defined as 2 quantifiable (≥LLOQ) qRT-PCR measurements (reported on 2 or more independent samples over 2 days), from Day 1 (pm) up to Day 8 (am).
Per protocol (PP) analysis set	All participants randomised, having received IMP (CD388/placebo), challenged with the study virus, who have a valid result for at least 80%

Participant Analysis Set	Description
	of the planned qRT-PCR nasal samples from Day 1 (pm) up to Day 8 (am), i.e., at least 11 out of 14, and present no major deviations likely to impact the evaluation of the primary efficacy endpoint. All deviations and all cases with at least one qRT-PCR result missing will be reviewed during the blinded data review meeting (BDRM) and adjudicated as belonging to the PP set or not.
Safety analysis set	All participants randomly assigned to study intervention and who received study intervention. Participants will be analysed according to the intervention they actually received.
PK analysis set	All participants randomly assigned to study intervention with at least 1 post-dose PK result.

Membership of participants in each analysis set will be determined at a planned data review meeting, prior to any analysis and database lock.

The primary efficacy analysis will be on the PP analysis set. The ITT and ITT-I analysis set will be used for supportive analyses on all or part of the primary and secondary efficacy endpoints, as defined in the SAP. The safety evaluation will be performed on the safety analysis set. Additional analysis sets may be defined in the SAP.

9.4. Statistical Analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Data will be analysed and reported using SAS® version 9.4 or later.

9.4.1. Statistical Analysis Plan

The SAP will be developed and finalised prior to the first interim analysis for the study. The finalised SAP will be signed prior to unblinding the interim analysis data. The SAP will provide a more technical, detailed, and comprehensive description of the statistical analyses that will be computed, expanding on the protocol specified analysis.

Any deviation(s) from the original statistical plan outlined in the protocol will be described and justified in an amendment to the protocol and/or SAP, as appropriate, and referenced in the final clinical study report.

Further post-hoc evaluations of any exploratory endpoints may be conducted and reported separately.

9.4.2. General Considerations

9.4.2.1. Descriptive Statistics

Continuous variables will be summarised using number of available data, number of missing data, mean (and/or geometric mean, where applicable), standard deviation, median, lower quartile, upper quartile, minimum, and maximum values. When relevant, confidence intervals (CIs) will be computed for the mean and/or the median.

Categorical variables will be summarised using number of available data, number of missing values, frequency counts for each category and corresponding percentage. Percentages will be calculated using the number of available data as the denominator (i.e., not including missing values). When relevant, CIs will be computed. If not otherwise specified in the SAP, the Wilson Score Method will be used to compute CIs for proportions.

9.4.2.2. Inferential Statistics and Significance Testing

Between-arm comparisons will be performed using appropriate hypothesis tests at the 2.5% 1-sided significance level, except if otherwise specified. No adjustment of the type-1 error rate for multiple comparisons will be done and each test will use a nominal level of 0.025 1-sided.

For continuous variables (either raw data or log-transformed data) the difference in means, the standard error and the 95% 2-sided CI will be presented. In case of log-transformed variables, in addition to the previous statistics on the log-transformed data, the geometric means and geometric mean ratio and its 95% 2-sided CI for the original variable will be presented. The Wilcoxon rank-sum test, t-test, or analysis of covariance will be used, depending on whether the endpoints are normally distributed. Details on the method used for each endpoint will be provided in the SAP. Methods for checking statistical model assumptions and alternative methods of analysis if the assumptions are not fulfilled will be described in the SAP.

For categorical variables, differences in absolute frequency and/or relative risks will be presented, with their 95% 2-sided CIs. Except otherwise specified in the SAP, the Fisher exact test will be used to compare frequencies between study intervention arms.

9.4.3. Planned Analysis

9.4.3.1. Participant Accountability

The number of participants receiving challenge agent, receiving IMP (CD388/placebo), withdrawing from (also split by reason for withdrawal), and completing the study, and the numbers in each analysis set, will be summarised.

9.4.3.2. Protocol Deviations

Participant's data will be reviewed for major protocol deviations prior to database lock at a planned BDRM, and decisions will be documented within the meeting minutes. At this meeting, participants will be reviewed for their inclusion/exclusion from the analysis sets.

9.4.3.3. Demographic and Baseline Characteristics

Descriptive statistics of demographics (age, sex, height, body weight, BMI, and ethnicity) will be presented by study intervention arm and across all participants. Medical history information will be listed. Other baseline characteristics will be defined in the SAP.

9.4.3.4. Compliance to Study Intervention

Compliance with IMP (CD388/placebo) will be computed for each study intervention arm as proportion of participants actually receiving a full dose of IMP as prescribed.

9.4.4. Primary Efficacy Analysis

The primary endpoint (VL-AUC of influenza challenge virus as determined by qRT-PCR on nasal samples starting a day post viral challenge [Day 1, pm] up to Day 8 [am], [i.e., virology]), will be analysed on the PP analysis set.

The calculation of the VL-AUC will be performed on log_{10}-transformed PCR data using the trapezoidal summation rule based on actual time intervals in hours.

Descriptive statistics for the mean and median and the 2-sided 95% CI for the mean will be presented by study arm. The significance of the difference between each CD388 arm and the placebo arm will be analysed using the Wilcoxon rank-sum test. The estimator of the difference in area under the curve (AUC), with 95% CI will be obtained via the Hodges-Lehman (+Moses) method. The one-sided p-value will be presented. No adjustment of the type-1 error rate for multiple comparisons will be performed and each test will use a nominal level of 0.025 1-sided. Further details will be described in the SAP.

The analysis will be repeated on the ITT analysis set as a sensitivity analysis.

9.4.5. Secondary Efficacy Analysis

Secondary endpoints as outlined in Section 3, Objectives and Endpoints, will be summarised by study intervention arm as described in Table 9-2. Further details will be provided in the SAP.

Table 9-2: Methods for Analysis of Secondary Efficacy Endpoints

Endpoint	Analysis
Peak viral load by qRT-PCR	Descriptive statistics for continuous variables (see Section 9.4.2.1). Inferential analysis: Wilcoxon rank-sum test.
Time to confirmed negative test by qRT-PCR	Descriptive statistics for continuous variables (see Section 9.4.2.1). Kaplan-Meier curves No inferential analysis
VL-AUC by viral culture Peak viral load by viral culture	Descriptive statistics for continuous variables (see Section 9.4.2.1). Inferential analysis: Wilcoxon rank-sum test.
Time to confirmed negative test by viral culture	Descriptive statistics for continuous variables (see Section 9.4.2.1). Kaplan-Meier curves No inferential analysis
TSS-AUC Peak TSS	Descriptive statistics for continuous variables (see Section 9.4.2.1). Inferential analysis: Wilcoxon rank-sum test.

Endpoint	Analysis
Peak daily symptom score	Descriptive statistics for continuous variables (see Section 9.4.2.1). Inferential analysis: Wilcoxon rank-sum test on each day.
Time to symptom resolution	Descriptive statistics for continuous variables (see Section 9.4.2.1). Kaplan-Meier curves Inferential analysis: Wilcoxon rank-sum test.
Incidence of confirmed influenza infection, defined as 2 quantifiable (≥LLOQ) qRT-PCR measurements (reported on 2 or more independent samples over 2 days)	Descriptive statistics for categorical variables (see Section 9.4.2.1). Inferential analysis: Fisher exact test.
Incidence of occurrence of at least 1 positive quantitative (≥LLOQ) cell culture	
Incidence of RT-PCR-confirmed symptomatic influenza infection, definition 1 (2 quantifiable qRT-PCR measurements [reported on 2 or more independent samples over 2 days]) AND symptoms ≥2 at a single time point	
Incidence of RT-PCR-confirmed moderately severe symptomatic influenza infection, definition 2 (2 quantifiable qRT-PCR measurements [reported on 2 or more independent samples over 2 days]) AND any symptoms of grade ≥2 at a single time point	
Incidence of culture lab-confirmed symptomatic influenza infection (1 quantifiable [≥LLOQ] cell culture measurement AND symptoms ≥2 at a single time point)	

9.4.6. Tertiary/Exploratory Analysis

Tertiary/exploratory endpoints as outlined in Section 3, Objectives and Endpoints, will be summarised by study intervention arm, as applicable. Further details are described in the SAP.

9.4.7. Safety Analyse(s)

All safety analyses will be computed on the safety analysis set.

Unless otherwise stated, safety endpoints will be presented in terms of descriptive statistics only.

Adverse events will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) that is current at time of study start and summarised descriptively by SOC, PT, and study intervention arm for the number of AEs and treatment-emergent (relative to inoculation and separately relative to IMP administration) AE reported and the number and percentage of participants reporting each AE and treatment-emergent (relative to inoculation and separately relative to IMP administration) AE.

[redacted]

9.4.8. Pharmacokinetic Analysis

Descriptive statistics will be calculated for the plasma concentrations of CD388 at each applicable time point and for the derived plasma PK parameters. Statistics include sample size (n), mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum.

For each participant, plasma concentration-time data of CD388 will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced.

Additional PK analyses may be performed as deemed necessary.

The details of the PK analyses will be provided in a separate PK analysis plan.

9.5. Interim Analysis

A first interim analysis will be performed, by an unblinded team not involved in daily management of the study, for participants in Cohort 1 who have completed the inpatient phase at the time the interim analysis is performed. An optional second interim analysis may be performed by an unblinded team not involved in daily management of the study, within Cohort 2, depending on the outcome of the first interim analysis (see Figure 4-1).. Summary results of each interim analysis will inform on:

- The participant numbers per study arm.
- The CD388 dose levels to be studied (Section 6.6, Dose Modification).
- The number of CD388 dose levels to be studied.

The SAP will describe the planned interim analyses in greater detail.

9.6. Data Monitoring Committee

Not applicable.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines.
- Applicable ICH Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

In addition to regulatory submission, the protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an REC by the PI/investigator and reviewed and approved by the REC before the study is initiated.

Substantial amendments to the protocol will require regulatory authority and REC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The PI/investigator will be responsible for the following:

- Providing written summaries of the status of the study to the REC annually, or more frequently, in accordance with the requirements, policies, and procedures established by the REC.
- Notifying the REC of SAEs or other significant safety findings as required by REC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the REC, the REC, UK SI 2004/1031 The Medicines for Human Use (Clinical Trials) Regulations, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.1.3. Confidentiality

The PI/investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

10.1.4. Informed Consent Process

The trained and delegated study staff competent to perform the informed consent procedure will obtain a signed study-specific ICF from each participant before any study-specific procedures are performed.

Historical screening data may be collected through the hVIVO generic screening process, which is a comprehensive assessment of health status including previous medical history. For assessments taken under the hVIVO generic screening, a separate informed consent is obtained.

When historical screening data collected through the hVIVO generic screening process is used for screening, the study-specific ICF will be obtained at the first study-specific visit from each participant before any study-specific procedures are performed.

Potential participants will typically be sent a copy of the REC approved study-specific ICF at the time of invite to the first study-specific visit and at least a day prior to the visit and will be encouraged to read it prior to their appointment. Upon arrival at the screening visit/quarantine admission visit (as applicable), the study-specific ICF is discussed by the trained and delegated study staff competent to perform the informed consent procedure, and the participants will be given the opportunity to ask any questions and may take the information sheet away to consider their participation.

All participants will be required to have a good understanding of English and the PI/investigator will be responsible for ensuring that the participant understands the information contained in the ICF. Once the PI/investigator has confirmed that the participant has capacity and has understood the study, including the benefits and risks of participation, the participant and the PI/investigator or authorised designee can sign and date the study-specific ICF.

The study-specific ICF must be signed and dated by the participant and countersigned by the trained and delegated study staff competent to perform the informed consent procedure (whoever conducted the consent discussion). A copy of the study-specific ICF will be given to the participant, and the original will be held in the hVIVO trial master file.

Participants will be assured that they can withdraw from the study at any time and for any reason without prejudice to their future medical care, and that they will be informed in a timely manner if new information becomes available that may affect their willingness to continue their participation in the study. This information will be included within in the study-specific ICF.

The study-specific ICF will contain a separate section that addresses the use of samples for future research. The PI/investigator or authorised designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate (with no requirements to disclose the reason for withdrawal) and may withdraw their consent at any time and for any reason.

A separate ICF for genetic testing of samples will be required to document a participant's agreement to allow any specimens to be used for related exploratory genetic research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.5. Data Protection

Participants will be assigned a unique identifier by hVIVO. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant in ICF.

The participant must be informed that his/her medical records may be examined by clinical QA auditors or other authorised study staff appointed by the sponsor, by appropriate REC members, and by inspectors from regulatory authorities.

10.1.6. Committee(s) Structure

This study will not include an early safety data review. However, participant safety will be continuously monitored by the SME/medical monitor which includes safety signal detection at any time during the study.

10.1.7. Dissemination of Clinical Study Data

The key design elements of this protocol will be posted on publicly accessible registry. A 'public registry' is defined as any register on the World Health Organisation list of primary registries or the International Committee of Medical Journal Editors list of registries, e.g., ClinicalTrials.gov or International Standardised Randomised Controlled Trial Number registry.

It is the sponsor's (or sponsor delegate) responsibility to send the Clinical Trial Summary Report to the REC and MHRA (if required) within 1 year of the end of the study, and where applicable, to publish the summary results within 1 year of the end of the study in the public register(s) where the clinical study was registered.

[redacted]
hVIVO have a legal obligation to protect at all times the confidentiality of participant personal data from the point of capture, through processing, dissemination in line with consent from the participant and to its final disposition.

10.1.8. Data Quality Assurance

Participant data will be collected at site using paper source casebooks which will then be data entered into the eCRF database unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The PI/investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The PI/investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. This can be paper source and/or eSource.

The PI/investigator must permit study-related monitoring, audits, REC review, and regulatory agency inspections and provide direct access to source data documents. [redacted]

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised investigator site staff are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

[redacted]

10.1.9. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. [redacted]

10.1.10. Study Discontinuation

The sponsor reserves the right to temporarily suspend or terminate the study for any reason at any time. In addition, the study may be temporarily suspended or terminated at any time if, in the opinion of the PI/investigator, the safety data suggest that the medical safety of participants is being compromised.

If the study is suspended or terminated for safety reason(s), the sponsor will promptly inform the PI/investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action.

[redacted]

Termination of the clinical study may also be initiated by the MHRA or the REC.

10.1.11. Publication Policy

By signing the study protocol, the PI/investigator agrees that the results of this study may be used for the purposes of national and international registration, for publication, and as information for medical and pharmaceutical professionals by the sponsor.

If necessary, the authorities will be notified of the PI/investigator's name, address, qualifications, and extent of involvement. To allow the use of the information derived from this clinical study, the PI/investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the sponsor.

If the study is to be published, the sponsor and hVIVO may jointly prepare and co-author manuscript(s) that could result from the clinical study. In the case the sponsor acts as fully responsible for the publication, the sponsor agrees to allow the PI/investigator time to review all manuscripts and abstracts prior to submission for publication. The sponsor reserves the right to include the report of this study in any regulatory documentation or submission or in any informational materials. The sponsor also reserves the right to delete any confidential information from any proposed manuscripts prior to submission for publication. Confirmation of study-specific arrangements can be found in the clinical study agreement.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the sponsor.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10-1 will be performed by the local laboratory.

Study-specific requirements for inclusion or exclusion of participants are detailed in Section 5, Study [redacted]

[redacted]

[redacted]

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

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

[redacted]

[redacted]

[redacted]

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Adverse Event

[redacted]

Events Meeting the AE Definition

- [redacted]
- [redacted]

Events Meeting the AE Definition

- [redacted]

Events NOT Meeting the AE Definition

- [redacted]

10.3.2. Adverse Drug Reaction

An adverse drug reaction is any untoward and unintended response in a participant to an IMP which is related to any dose administered to that participant.

'Response' in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

All AEs assessed by either the reporting PI/investigator or the sponsor as having a reasonable causal relationship to an IMP qualify as adverse drug reactions. The expression 'reasonable causal relationship' means to convey in general that there is evidence or argument to suggest a causal relationship.

10.3.3. Unexpected Adverse (Drug) Reaction

An "Unexpected Adverse (Drug) Reaction" means an adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:

(a) In the case of a product with a marketing authorisation, in the Summary of Product Characteristics for that product,

(b) In the case of any other IMP, in the Investigator's Brochure relating to the study in question.

10.3.4. Serious Adverse Event

SAE Definition
An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening [redacted]
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation • [redacted]
d. Results in persistent disability/incapacity • [redacted]

- [redacted]

e. Is a congenital anomaly/birth defect

f. Is an important medical event

- [redacted]

- [redacted]

10.3.5. Suspected Unexpected Serious Adverse Reaction

A SUSAR is a serious adverse reaction, the nature and severity* of which is not consistent with the information about the medicinal product in question, as defined in the Investigator's Brochure relating to the study in question.

[redacted]

10.3.6. Recording, Assessment, and Follow-up of Adverse Events/Serious Adverse Events

10.3.6.1. Adverse Event/Serious Adverse Event Recording

All AEs/SAEs will be collected from the time of written study-specific informed consent until study completion/final study contact or until the resolution of the AE. [redacted]

[redacted]

10.3.6.2. Assessment

Description

[redacted]

Onset and end

The dates and times of the onset and end of the event should be recorded.

Assessment
Challenge Agent-related Symptoms [redacted]
Physical Examination [redacted]
Symptom-directed Physical Examination [redacted]
Vital Signs [redacted]
Temperature [redacted]
Spirometry [redacted]

Laboratory Values

[redacted]

C-reactive Protein

[redacted]

10.3.6.3. Assessment of Intensity

The term 'severe' is often used to describe the intensity (severity) of a specific event. This is not the same as 'serious' which is based on participant/event outcome or action criteria.

The PI/investigator will use the DAIDS table as a reference when collecting, reporting, and clarifying database queries of AEs, SAEs, and adverse reactions.

The severity of an AE that does not appear in the DAIDS table should be determined according to the definitions in Table 10-2.

Table 10-2: Classification of Adverse Event Severity

Grade	Classification	Definition
Grade 1	Mild	Mild level of discomfort, and does not interfere with regular activities
Grade 2	Moderate	Moderate level of discomfort and significantly interferes with regular activities
Grade 3	Severe	Significant level of discomfort and prevents regular activities
Grade 4	Life threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalisation or hospice care probable

Grade	Classification	Definition
Grade 5	Death	Death

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.3.6.4. Frequency

[redacted]

- [redacted]
- [redacted]
- [redacted]

10.3.6.5. Assessment of Causality

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Table 10-3: Classification of Adverse Event Relationship

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

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

10.3.6.6. Action Taken

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

10.3.6.7. Outcome

An AE/SAE should be followed until the PI/investigator has determined and recorded the outcome. The outcome should be classified according to the categories shown in Table 10-4.

Table 10-4: Classification of Adverse Event Outcome

Classification	Definition
Resolved	[redacted]
Resolved with sequelae	[redacted]
Ongoing	[redacted]
Fatal	[redacted]
Unknown (e.g., lost to follow-up)	[redacted]

10.3.6.8. Follow-up

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

10.3.7. Reporting of Serious Adverse Events

Serious AEs must be documented and reported as per hVIVO SOPs.

Prompt notification of SAEs by the PI/investigator to the sponsor is essential so that the sponsor can meet its reporting obligations for the study.

[redacted]

[redacted]

[redacted]

[redacted].

[redacted]

[redacted]

[redacted]

[redacted]

10.3.8. Reporting of Suspected Unexpected Serious Adverse Reaction

[redacted].

10.3.9. Adverse Reactions to Non-investigational Medicinal Products

[redacted]

10.3.10. Pregnancy

[redacted]

[redacted].

[redacted]

- [redacted]

- [redacted]

10.4. Appendix 4: Normal Ranges

[redacted]

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

[redacted]

ECG[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted] [redacted]	[redacted]

[redacted]

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

[redacted]

10.5. Appendix 5: Genetics

Use/Analysis of Deoxyribonucleic Acid

[redacted]

10.6. Appendix 6: Abbreviations

Abbreviation	Term
ADA	Anti-drug antibody
AE	Adverse event
AP	Analytical plan
AUC	Area under the curve
AUC_{0-t}	Area under the plasma 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
β-hCG	β-human chorionic gonadotrophin
BMI	Body mass index
(c)GMP	(current) Good Manufacturing Practice
CI	Confidence interval
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus Disease 2019
DAIDS	Division of AIDS
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
(e)CRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERS	European Respiratory Society
Fc	Crystallisable fragment
FDA	Food and Drug Administration
$FEV_{(1)}$	Forced expiratory volume (in 1 second)
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GAD-7	Generalised Anxiety Disorder-7
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GP	General practitioner
HAI	Haemagglutination inhibition
HbA1c	Haemoglobin A1c
HIV	Human immunodeficiency virus
HVC	Human viral challenge
ICF	Informed consent form
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational medicinal product
ITT	Intent-to-treat

ITT-I	Intent-to-treat infected
LRT	Lower respiratory tract
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger RNA
NA	Neuraminidase
NAI	Neuraminidase inhibitor
NOAEL	No-observed-adverse-effect level
PCR	Polymerase chain reaction
PHQ-9	Patient Health Questionnaire-9
PI	Principal investigator
PK	Pharmacokinetic(s)
PP	Per protocol
PT	Preferred term
PV	Pharmacovigilance
QA	Quality assurance
(q)RT-PCR	(Quantitative) reverse transcriptase-polymerase chain reaction
REC	Research Ethics Committee
RNA	Ribonucleic acid
RTI	Respiratory tract infection
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SME	Sponsor's medical expert
SOC	System organ class
SoE	Schedule of events
SOP	Standard operating procedure
SUSAR	Suspected unexpected adverse reaction
TBD	To be determined
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum plasma concentration
TSS	Total symptoms score
TSS-AUC	Area under the curve over time of total symptoms score
UK	United Kingdom
URT	Upper respiratory tract
VL-AUC	Area under the viral load-time curve

10.7. Appendix 7: Definitions

10.7.1. General

TERM	hVIVO Services Limited Definition
Completion (of a participant's participation in the study)	A participant will be considered to have completed the study after his/her attendance at the last planned study visit or the last unscheduled visit, as applicable.
Baseline	For safety assessments the nearest assessments completed prior to IMP dosing (and inoculation where appropriate) will be used as the baseline measure, unless stated otherwise.
Enrolment (of a participant into the study)	A participant will be considered to be 'enrolled' into the study once he/she has been randomised. Potential participants who are screened for the purpose of determining suitability for the study, but do not participate in the study, are not considered enrolled.
Infectious titre	The titre of inoculum producing viral infection in a participant. The term 'titre' applies to the quantity or concentration of inoculum (depending on the units documented).
Quarantine group	A group of participants who are admitted to and are resident in the quarantine unit for a particular quarantine period (i.e., participants whose Day 0 and scheduled discharge date are the same).
Quarantine period	The period when clinical study participants are isolated in the quarantine unit during an HVC study.
Randomisation number	The number allocated to a participant at randomisation, generated as stated in the protocol (NB. Not applicable will be recorded for "screen fail" participants or participants who are not randomised).
Subject number	The unique number assigned to a subject in the hVIVO subject database, which is used to identify the subject prior to randomisation. This number will be used throughout the recruitment and generic screening process to identify the subject.
Challenge	The inoculation of a participant with challenge agent inoculum. By definition, the day of challenge is Day 0.

10.7.2. Study Definition of Infection and Illness

TERM	CRITERIA (RESPIRATORY SYNCYTIAL VIRUS, HUMAN RHINOVIRUS, AND INFLUENZA STUDIES)
The following definitions should only be applied to data collected from Day 1 onwards	
Lower respiratory tract (LRT) illness	Any one of the following signs and/or symptoms on 2 consecutive scheduled assessments, at least one of which must feature grade 2 severity, or if any of the following attain grade 3 severity once: • Self-reported symptoms: cough, shortness of breath, chest tightness and wheeze. • Physician findings: Abnormal breath sounds externally (e.g., stridor, wheezing) and on chest auscultation (rhonchi, crepitations or other).
Upper respiratory tract (URT) illness	Any one of the following signs and/or symptoms on 2 consecutive scheduled assessments, at least one of which must feature grade 2 severity, or if any of the following attain grade 3 severity once: • Self-reported symptoms: rhinorrhoea (runny nose), nasal congestion (stuffy nose), sore throat, sneezing. • Physician findings: nasal discharge, otitis, pharyngitis, sinus tenderness.
Systemic illness	Fulfils the criteria for febrile illness, or fulfils the definition of URT illness and/or LRT illness, **and** any one of the following symptoms on 2 consecutive scheduled assessments, at least one of which must feature grade 2 severity, or if any of the following attain grade 3 severity once: • malaise • headache • muscles and/or joint ache • chilliness • feverishness
Febrile illness	Any occurrence of temperature ≥37.9ºC.
Laboratory-confirmed influenza infection	Viral shedding definition has been met.

10.7.3. Study Definition of a Postmenopausal Woman

Amenorrhea for >12 Months with No Alternative Medical Cause	Appropriate Age[a]	Single FSH Value Level >40 mIU/mL[b]	Meets Study Definition of Postmenopausal Female Participant
Yes	Yes	Yes	Yes
No	Yes	Yes	No[c]
Yes	Yes	No	Yes
No	No	Yes	No

[a] 45 years and above.

[b] Serum FSH level must be taken in the absence of combined hormonal contraception or hormone replacement therapy.

[c] If there is less than 12 months of amenorrhea a single raised FSH value is insufficient however, relevance of this for particular studies can be justified depending on nature of the IMP and at the discretion of the PI/investigator. Note: If consecutive FSH tests are required these should be carried out on 2 separate blood samples taken at least 4 to 6 weeks apart.

10.8. Appendix 8: Protocol Amendment History

Protocol History			
Version	**Date**	**Amendment Type and Number**	**Description of Change**
2.0	18/Jul/2022	N/A	Initial Clinical Trial Protocol
3.0	14/Sep/2022	Non-Substantial Amendment 01	Administrative changes made to the challenge route. Schedule of Events (SOE) updated to clarify ADA requirements, Directed Physical Examination updated to mandatory for Day 2, Day 3 and Day 4 and updated to include cardiac enzyme assessment. Section 6.3, updated to reflect use of interactive Web Response (IWRS). Section 8.3.4, Respiratory Tract Infection Surveillance updated to use of an e-diary and process of follow up by investigator staff. Section 8.4, updated to clarify when the symptom-directed physical examination will be conducted Section 8.4.3, updated to include a grading scale to assess local reactions of injectable products. Section 10.3, Solicited AEs updated for clarity Other minor changes to formatting

4.0	06/Oct/2022	Non-Substantial Amendment 03	Section 1, Protocol Synopsis, Summary of Study Design, Randomisation and Sample Size Determination and Section 9.2, Sample Size Determination, updated to reflect the modified randomisation schedule. Section 1, Protocol Synopsis, Summary of the Study Design and Section 4.1, Overall Design updated to remove the following paragraph "*Depending on emerging PK data from the ongoing Phase 1 study (CD388.IM.SQ.1.01), IMP administration may instead occur on a day between Day -7/-6 and Day -2. In these cases, the timing of procedures and the admission day to quarantine would be altered accordingly.*" This statement is no longer applicable, dose confirmed as D-5 following Phase I data. Section 4.1, Overall Design and Section 6.3, Randomisation and Blinding updated to reflect up to of Arm 1 and Arm 2 sample size of up to 30. Figure 4-1: Overview of study design updated to reflect the modified randomisation schedule. Section 1, Protocol Synopsis, Summary of Study Design, 1.1 study schematic, 1.2 Schedule of Events and Section 4.1, Overall Study Design update to include D-7 as an additional admission day. Section 2, Protocol, Summary of Study Design, Statistics, Section 4.1, Overall Design, Section 7.6, Adaptive Features, Table 7-2 and Section 9.5, Interim Analysis updated to highlight enrolment will not be halted at the time the first interim analysis is performed. Participants in Cohort 1 who have completed the inpatient phase at the time the interim analysis is performed will be included in the first interim analysis. This update is to supplement enrolment for cohort 1. Section 10.3, Solicited AEs, updated to reflect correct PI assessment for symptoms. Other minor administrative changes made, including correction of typos.

11. References

Bueno de Mesquita PJ, Nguyen-Van-Tam J, Killingley B, Enstone J, Lambkin-Williams R et al. Influenza A (H3) illness and viral aerosol shedding from symptomatic naturally infected and experimentally infected cases. Influenza Other Respir Viruses. 2021;15(1):154-163.

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events. Corrected Version 2.1. July 2017.

Fragaszy EB, Warren-Gash C, Wang L, Copas A, Dukes O, Edmunds WJ et al.; Flu Watch Group. Cohort Profile: The Flu Watch Study. Int J Epidemiol. 2017;46(2):e18.

Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Society technical statement. American Journal and Critical Care Medicine. 2019;200(8):70-88.

Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet. 2018;391(10127):1285-1300.

Lambkin-Williams R, Noulin N, Mann A, Catchpole A, and Gilbert AS. The human viral challenge model: accelerating the evaluation of respiratory antivirals, vaccines, and novel diagnostics. Respir Res. 2018;19:123.

Nguyen-Van-Tam JS, Killingley B, Enstone J, Hewitt M, Pantelic J, Grantham ML et al. EMIT Consortium. Minimal transmission in an influenza A (H3N2) human challenge-transmission model within a controlled exposure environment. PLoS Pathog. 2020;16(7):e1008704.

Nunes B, Viboud C, Machado A, Ringholz C, Rebelo-de-Andrade H et al. Excess mortality associated with influenza epidemics in Portugal, 1980 to 2004. PLoS One. 2011; 6:e20661.

Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL et al. Multi-ethnic reference values for spirometry for the 3–95 year age range: the global lung function 2012 equations. Report of the Global Lung Function Initiative (GLI), European Respiratory Society (ERS) Task Force to establish improved lung function reference values. Eur Respir J. 2012;40(6):1324–1343.

Ramos-Sevillano E, Wade WG, Mann A, Gilbert A, Lambkin-Williams R et al. The Effect of Influenza Virus on the Human Oropharyngeal Microbiome. Clin Infect Dis. 2019;68(12):1993-2002.

Shieh G, Jan SL, and Randles RH (2006). On power and sample size determinations for the Wilcoxon–Mann–Whitney test. Journal of Nonparametric Statistics. 2006;18(1):33-43.

Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB et al. Influenza-associated hospitalizations in the United States. JAMA. 2004;292:1333-1340.

Xu X, Blanton L, Elal AIA, Alabi N, Barnes J et al. Update: Influenza Activity in the United States During the 2018-19 Season and Composition of the 2019-20 Influenza Vaccine. MMWR Morb Mortal Wkly Rep. 2019;68(24):544-551.

Yogaratnam J, Rito J, Kakuda TN, Fennema H, Gupta K et al. Antiviral Activity, Safety, and Pharmacokinetics of AL-794, a Novel Oral Influenza Endonuclease Inhibitor: Results of an Influenza Human Challenge Study. J Infect Dis. 2019;219(2):177-185.

Zucs P, Buchholz U, Haas W, and Uphoff H. Influenza associated excess mortality in Germany, 1985-2001 Emerg Themes Epidemiol. 2005;2:6.