CLINICAL STUDY PROTOCOL

A RANDOMISED, PHASE 1B, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND ANTIVIRAL ACTIVITY OF RV299 AGAINST RESPIRATORY SYNCYTIAL VIRUS IN THE VIRAL CHALLENGE MODEL

Short Title:	Safety, pharmacokinetics, and antiviral activity of RV299 against respiratory syncytial virus (RSV)
Version and Date of Protocol:	Final version 3.0, 31Oct2022
Sponsor:	ReViral Limited Stevenage Bioscience Catalyst Gunnels Wood Road Stevenage SG1 2FX United Kingdom (UK)
Sponsor Protocol Number:	REVD002
hVIVO Protocol Number:	VIR-CST-001
Compound Number:	RV299
IRAS ID:	1005624

Confidentiality and Protections Statement:

Sponsor Statement

This protocol 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:

PPD

November 3, 2022

PPD , **MBBCh, MBA**

PPD PPD

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): Dr PPD

Signature: PPD

Date: 04 NOV 2022

(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	ReViral Limited Stevenage Bioscience Catalyst Gunnels Wood Road Stevenage SG1 2FX United Kingdom (UK)
Sponsor's representative	PPD ReViral Inc. PPD
Principal investigator and Clinical Study Unit	Dr, PPPD PPD
Sponsor's medical expert	Dr PPD ReViral Limited PPD
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Key protocol contributors	Refer to the local study contact list document

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1. Protocol Synopsis

Protocol Title	A randomised, Phase 1b, double-blind, placebo-controlled study to evaluate the safety, pharmacokinetics (PK), and antiviral activity of RV299 against respiratory syncytial virus (RSV) in the viral challenge model
Short Title	Safety, PK, and antiviral activity of RV299 against RSV
Protocol number	REVD002/VIR-CST-001
Sponsor	ReViral Limited
Clinical phase	1b
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	Treatment of RSV infection
Design	This is a randomised, Phase 1b, double-blind, placebo-controlled proof-of-concept, study of orally administered RV299 in an RSV viral challenge model

Objectives and Endpoints

Objectives	**Endpoints**
Primary:	
Efficacy	
• To assess the antiviral activity of RV299 compared to placebo in healthy adult participants infected with RSV-A Memphis 37b.	• The area under the curve (AUC) for RSV viral load measured in nasal washes by quantitative real time reverse transcription polymerase chain reaction (qRT-PCR) in participants inoculated with RSV-A Memphis 37b, starting at initial administration of investigational medicinal product (IMP) up to planned discharge from quarantine (Day 12, am).
Secondary:	
Efficacy	
• To evaluate the effect of RV299 compared to placebo in healthy adult	Additional viral load endpoints relating to antiviral effect include, but are not limited to:

participants inoculated with RSV in terms of antiviral effect assessed by: ○ Viral-load related endpoints.	• Peak viral load of RSV as defined by the maximum viral load determined by qRT-PCR measurements in nasal samples starting from initial administration of IMP up to planned discharge from quarantine (Day 12, am). • Time (days) to confirmed negative test by qRT-PCR measurements in nasal samples starting at initial administration of IMP to first confirmed undetectable assessment after peak measure. • Time (days) to confirmed negative test by qRT-PCR measurements in nasal samples starting from peak qRT-PCR after initial administration of IMP to first confirmed undetectable assessment after peak measure. • Time (days) to peak qRT-PCR in nasal samples, starting from initial administration of IMP. • Area under the viral load-time curve (VL-AUC) of RSV challenge virus as determined by viral culture on nasal samples, starting at initial administration of IMP up to planned discharge from quarantine (Day 12, am). • Peak viral load of RSV as defined by the maximum viral load determined by viral culture measurements in nasal samples starting from initial administration of IMP up to planned discharge from quarantine (Day 12, am). • Time (days) to confirmed negative test by viral culture measurements in nasal samples starting at initial administration of IMP to first confirmed undetectable assessment after peak measure. • Time (days) to confirmed negative test by viral culture measurements in nasal samples starting from peak viral culture after initial administration of IMP to first confirmed undetectable assessment after peak measure.
• To evaluate the effect of RV299 compared to placebo in healthy adult participants inoculated with RSV in terms of antiviral effect assessed by: ○ Clinical symptom-related endpoints.	Clinical symptom-related endpoints include, but are not limited to: • Area under the curve over time of total clinical symptoms (TSS-AUC) as measured from 10 symptoms within the graded symptom scoring system collected 3 times daily starting at initial administration of IMP up to planned discharge from quarantine (Day 12, am).

	• Area under the curve over time of total clinical symptoms change from baseline (TSS-AUC-CFB) as measured from 10 symptoms within the graded symptom scoring system collected 3 times daily starting at initial administration of IMP up to planned discharge from quarantine (Day 12, am). • Peak symptoms diary card score: peak total clinical symptoms (TSS) as measured from 10 symptoms within the graded symptom scoring system collected 3 times daily starting from initial administration of IMP up to planned discharge from quarantine (Day 12, am). • Peak daily symptom score: individual maximum daily sum of symptom score from initial administration of IMP up to planned discharge from quarantine (Day 12, am). • Time (days) to symptom resolution as measured from 10 symptoms within the graded daily symptom scoring system starting at initial administration of IMP to time of returning to baseline score. • Time (days) to symptom resolution as measured from 10 symptoms within the graded daily symptom scoring system starting at peak symptoms after initial administration of IMP to time of returning to baseline score. • Time (days) to peak as measured from 10 symptoms within the graded daily symptom scoring system starting from initial administration of IMP to the time of peak daily symptom score.
• To evaluate the effect of RV299 on nasal discharge in healthy adult participants inoculated with RSV when compared to placebo.	• Total weight of mucus produced starting at initial administration of IMP up to planned discharge from quarantine (Day 12, am). • Total number of tissues used by participants starting at initial administration of IMP up to planned discharge from quarantine (Day 12, am).
Safety	
• To evaluate the safety of multiple orally administered doses of RV299 when compared to placebo.	• Safety data including, but not limited to, occurrence of adverse events (AEs) from initial administration of IMP up to the Day 28 follow-up. • Occurrence of serious AEs (SAEs) from initial administration of IMP up to the Day 28 follow-up.

• To monitor the safety of the challenge virus.	• Occurrence of AEs related to the viral challenge from viral challenge (Day 0) up to the Day 28 follow-up. • Occurrence of SAEs related to the viral challenge from viral challenge (Day 0) up to the Day 28 follow-up. • Use of concomitant medications from viral challenge (Day 0) up to the Day 28 follow-up.
Pharmacokinetics	
• To characterise the PK profile of RV299 after a single oral dose and after multiple oral doses in plasma from healthy participants inoculated with RSV.	Secondary endpoints related to PK include, but are not limited to: • Time to maximum plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve from time zero to the end of the dosing interval (AUC_{τ}), area under the plasma concentration-time curve over the last 24 hours dosing interval (AUC_{0-24h}) and area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$).
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[redacted]	[redacted]

*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 main study hypothesis is that treatment with RV299 will show an antiviral effect demonstrated by a significant reduction in RSV viral load AUC (measured by qRT-PCR) compared to placebo
IMP	RV299CCI [redacted] dosed twice daily (~12 hours interval) for 5 consecutive days (a total of 10 doses) Placebo to Match RV299CCI [redacted] dosed twice daily (~12 hours interval) for 5 consecutive days (a total of 10 doses)
Challenge agent	RSV-A Memphis 37b
Challenge agent route	Intranasally
Challenge agent titre	Approximately 4 $\log_{10}$ plaque-forming units (PFU).
Study population	Healthy adult male and female participants aged between 18 to 55 years, with a total body weight ≥50 kg and body mass index (BMI) ≥18 kg/m^2 and ≤35kg/m^2, who have been screened to be sero-suitable for infection with the RSV-A Memphis 37b virus 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 from 18 to 55 years of age, inclusive. The primary goal of this Phase 1b study is to assess the antiviral activity of RV299 against RSV in the viral challenge model. In addition, safety, tolerability, and PK of RV299 will be assessed. A total of 80 participants is planned to be enrolled in this study: 40 participants on RV299 and 40 participants on placebo. The study is divided into the following study phases: - **Screening phase**: from Day -90 to Day-3 pre-human viral challenge (HVC). 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 15 days (from Day -2 to Day 12). Procedures will include: • **Pre- HVC**: ○ Admission to quarantine unit on Day -2/-1. ○ Baseline assessments will be conducted as per Schedule of Events (SoE) up to Day 0, pre-challenge.

	• **HVC**: ○ RSV-A Memphis 37b virus inoculation on Day 0. • **Post-HVC**: ○ Randomisation to receive RV299 or matched placebo. ○ Administration of IMP (RV299/placebo). Each participant will receive IMP twice daily (~12 hours interval) for 5 consecutive days: ▪ IMP dosing to start on confirmation of RSV infection, i.e., after a positive result by qualitative integrative cycler polymerase chain reaction (qicPCR). The qicPCR of nasal wash will be performed twice daily on Days 2-5 (Day 5 morning only), or until a positive result is received, whichever is sooner. The earliest start of IMP dosing will be in the evening of Day 2 post-HVC (IMP will be initiated 12 hours ± 1-hour post nasal wash confirmation of infection) **OR** ▪ IMP would start in the evening of Day 5, if no positive result obtained by qicPCR ○ Day 1 onwards and each day – study assessments will be conducted as per SoE. ○ Participants will be discharged from the quarantine unit on Day 12 (or may remain longer at the discretion of the principal investigator [PI]/investigator). - **Outpatient phase:** • Final visit: Day 28 (±3 days).
Randomisation	1:1 to RV299 or matched placebo
Participant replacement policy	If a participant discontinues from study intervention OR withdraws from the study for reasons not related to AEs, a replacement participant may be enrolled if deemed appropriate by the PI/investigator and sponsor. The replacement participant will generally receive the same intervention as the participant being replaced. The replacement participant will be assigned a unique treatment/randomisation number.
Expected duration of participation per participant	Approximately 4 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 7 months from first participants planned first screening visit to the last participants last scheduled study visit.
End of study	The end of the study is defined as the date of the last visit of the last participant in the study.
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Statistics	Primary and secondary efficacy endpoints will be analysed descriptively. Continuous variables will be presented as mean with standard error of the mean (SEM) and median, and for log-transformed data the geometric mean with 95% 2-sided confidence interval (CI) will also be presented. For the primary and some secondary endpoints, formal statistical tests will be computed. The Chi-squared test or the Fisher Exact test will be used to compare proportions, and the t-test will be used to compare means across groups for continuous variables, when the underlying assumptions are fulfilled. For ordinal data and continuous data when the underlying assumptions for the t-test are not met, the Wilcoxon-Mann-Whitney test will be used to compare the distributions across treatment groups. S-Cubed will perform the statistical analysis for the study. Full details of the planned statistical analysis will be presented in the statistical analysis plan (SAP). Any deviations from the SAP will be documented in the clinical study report (CSR). **Study Analysis Sets:** The following analysis sets are defined for this study: • The intent-to-treat (ITT) analysis population, defined as all randomised participants who received challenge virus and at least 1 dose of IMP. • The intent-to-treat infected (ITT-I) analysis population, defined as all randomised participants who received challenge virus and at least 1 dose of IMP, and meet the criterion for laboratory-confirmed RSV infection. • The intent-to-treat infected analysis population A (ITT-A) is defined as all randomised participants who received challenge virus and at least 1 dose of IMP and meet the criterion for laboratory-confirmed RSV infection using only assessments prior to taking IMP. • The intent-to-treat infected analysis population B (ITT-B) is defined as all randomised participants who received challenge virus and at least 1 dose of IMP and meet the criterion for laboratory-confirmed RSV infection using only assessments after taking IMP.

	• The per protocol (PP) analysis population is defined as all ITT-I analysis population participants who have no major protocol deviations, and who completed the quarantine period up to the final day of quarantine (Day 12) and received all 10 doses of IMP. • The safety analysis population is defined as all randomised participants who received challenge virus and at least 1 dose of IMP. • The PK analysis population is defined as all ITT analysis population participants with at least one post-dose PK result. The primary efficacy analysis population will be the ITT-I analysis population, and the ITT-A, ITT-B, and the PP analysis populations will be used for sensitivity analyses. The safety evaluation will be performed on the safety analysis population.

1.1. Study Schematic: On-study Participant Progression

SCREENING PHASE	INPATIENT PHASE: QUARANTINE/ISOLATION, HUMAN VIRAL CHALLENGE, AND DOSING				OUTPATIENT PHASE
Day -90 to Day -3 Screening*	Day -2/-1 Admission to quarantine unit	Day 0 Inoculation with challenge agent & assessments as per Schedule of Events	Days 1 to 11 Dosing and assessments as per Schedule of Events	Day 12 Discharge from quarantine unit**	Follow-up visit: Day 28 (±3 days)

NOTES:

*Screening assessments (including repeats, as required), may be performed up to Day -2/-1, defined as the first study day (quarantine admission) at the discretion of the PI/investigator and in accordance with the design of the study.

**Release from quarantine is foreseen at Day 12 (12 days post inoculation) provided that, where appropriate, no virus is detected by qualitative virus antigen test or polymerase chain reaction (PCR) (negative virus antigen test or PCR below Ct cut-off) and the participant has no clinically significant symptoms. If the participant continues to have clinically significant symptoms and/or detectable virus on Day 12, additional extended quarantine stay may be required at the discretion of the PI/investigator.

1.2. Schedule(s) of Events (SoE)

Study Phase ➔	Screening Phase*	Inpatient Phase (Quarantine Isolation and Human Viral Challenge [HVC])																Clinic Visit Follow-up	Early Withdrawal
Study Day ➔ Procedure ↓	D -90 to D -3	D -2	D -1	D 0 Pre-HVC	D 0 HVC	D 0 Post-HVC	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D12 (Discharge)	D 28 (±3 days)	
Written informed consent (a)		X																		
Eligibility criteria (+)	X	X		X																
Medical & medication history	X	X																		
Demographics	X																			
Height & body weight, body mass index (BMI) (b)	X	X																(X)	(X)	(X)
Complete physical examination	X	X																X	X	X
Directed physical examination (incl. nasal)				(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)			
Vital signs (heart rate [HR], respiratory rate [RR], systolic blood pressure [BP], diastolic BP, oxygen saturation [SpO_2]) and tympanic membrane temperature	X	X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X											X				X		X	X
Spirometry	X																			
Patient Health Questionnaire (PHQ-9)	(X)	(X)																		
Generalised Anxiety Disorder Questionnaire (GAD-7)	(X)	(X)																		
Alcohol breath test	X	X																	X	
Urinalysis	X	X																X	X	X
Urine drugs of abuse and cotinine screen	X	X																	X	
Urine pregnancy test	X																	X	X	X
Symptom diary card (c)		(X)	3X	3X			3X	3X	3X	3X	3X	3X	3X	3X	3X	3X	3X	X		

Study Phase ➔	Screening Phase*	Inpatient Phase (Quarantine Isolation and Human Viral Challenge [HVC])																	Clinic Visit Follow-up	Early Withdrawal
Study Day ➔ Procedure ↓	D -90 to D -3	D -2	D -1	D 0 Pre-HVC	D 0 HVC	D 0 Post-HVC	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D12 (Discharge)	D 28 (±3 days)	
24-hour paper tissue collection & nasal discharge weight (d)			X	X			X	X	X	X	X	X	X	X	X	X	X	X		(X)
Product Administration																				
Randomisation								(X)	(X)	(X)	(X)									
RSV299/placebo dosing (k)								(X)	(2X)	(2X)	(2X)	(2X)	(2X)	(2X)	(2X)	(X)				
Challenge virus inoculation					X															
Collection Of Blood Samples																				
Serum follicle-stimulating hormone (FSH) (post-menopausal women)	X																			
Serum β-human chorionic gonadotrophin (β-hCG) pregnancy test (all females)		X																		
Blood Pharmacokinetics (e)								(X)	(X)	(X)	X	X	X	X	X	X	X	X		
Haematology (f)	X												X				X		X	X
Biochemistry (f)	X												X				X		X	X
Coagulation	X																			
Cardiac enzymes	X												X				X			
Thyroid function test	X																			
Serum markers of humoral immunity (g)	X																		X	X
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Study Phase ➔	Screening Phase*	Inpatient Phase (Quarantine Isolation and Human Viral Challenge [HVC])																Clinic Visit Follow-up	Early Withdrawal
Study Day ➔ Procedure ➔	D -90 to D -3	D -2	D -1	D 0 Pre-HVC	D 0 HVC	D 0 Post-HVC	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D12 (Discharge)	D 28 (±3 days)	
Collection Of Respiratory Samples																				
Nasopharyngeal swab - respiratory pathogen screen incl. SARS-CoV-2 (h)		X																		
Nasopharyngeal swab- RSV discharge test																	(X)	(X)		
Nasal wash – virology, viral genomics, CCI		X						2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X		
qicPCR (i)								2X	2X	2X	X									
Safety Assessments																				
Adverse event (AE) recording (j)		←																→		X
Concomitant medications (j)		←																→		X

KEY NOTES FOR TIME AND EVENTS SCHEDULE

(X)	The assessment may be optional, or at the PI's discretion. The PI may perform additional safety assessments as required.
X	Once daily, at approximately the same time each day, where applicable.
2X	Twice daily (~12 hours between assessments [± 1 hour]).
3X	Three times daily (at the same times each day [± 1 hour]).
*	Potential participants will be screened using the hVIVO generic screening process, and individuals who pass this screen will be admitted to the quarantine unit 1 to 2 days before challenge with study virus and provide study-specific informed consent. They will then be screened for eligibility for this study before viral challenge on Day 0. Results of tests or examinations performed under hVIVO generic screening process may be used to determine eligibility without the need to repeat the assessment if it is within 28 days prior to viral challenge/dosing with IMP.

+	Only the applicable inclusion/exclusion criteria will be reviewed at each time point.
a	Study-specific consent may occur on the day of admission, providing all required eligibility information has been collected through the Health Research Authority - approved hVIVO generic screening process.
b	Height will be taken at screening only.
c	After the baseline has been set, assessments will be performed at the same time each day (±1 hour from baseline) during quarantine. • Symptom diary card baseline: Day -1 (measurements on this day will be taken approximately 8 hours apart, ±1 hour). • Nasal wash baseline: Day 2 (sampling will be performed approximately 12 hours apart, ±1 hour).
d	Distribution of paper tissues and bags will start on Day -1, with the first collection on Day 0. Thereafter, collection of paper tissues will occur at the same time each day (±1 hour) with tissues distributed 24 hours ahead.
e	Blood Pharmacokinetics: plasma samples for RV299 assay will be collected as follows: • First dose (Dose 1): 0.5 hours pre-dose, and at the following hours post-first dose: 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8,10, 12, 24, 36, 48, 60, 72, 84 and 96 hours (note samples taken up to and including 10 hours post-dose should be taken at the indicated time point ±5 minutes. Samples taken thereafter at 12, 24, 36, 48, 60, 72, 84, and 96 hours post-first dose should be taken within the 30 minutes before the next IMP intake). • Last dose (Dose 10): 0.5 hours pre-dose, and at the following hours post-last dose: 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8,10, 12, 24, 36, 48, 60, 72, 84, and 96 hours (note samples taken up to and including 10 hours post-dose should be taken at the indicated time point ±5 minutes; samples taken thereafter should be taken at the indicated time point ±30 minutes). For participants who started dosing on Day 4, am, onwards, the 60-hour, 72-hour, 84-hour, or 96-hour timepoints after Dose 10 could occur after the participant has met the discharge criteria on Day 12. Thus, for a subset of participants, these timepoints could be after discharge. The guidance for the 60-hour, 72-hour, 84-hour, and 96-hour PK sample collection is as follows: • For participants who started dosing on Day 4, am, onwards, and who meet the discharge criteria on Day 12, the 60-hour, 72-hour, 84-hour, and 96-hour timepoint samples may be omitted, as applicable, if it occurs after discharge. • For participants who started dosing on Day 4, am, onwards, and who do not meet the discharge criteria on Day 12 the 60-hour, 72-hour, 84-hour, and 96-hour PK timepoint samples should be collected up to the point where participant meets the discharge criteria.
f	Blood will be drawn under non-fasted conditions. Repeat bloods may be drawn under fasted conditions if a lipid profile (triglyceride) or glucose is required (at the PI's discretion). All participants will be dosed under fasted conditions. For all doses, a pre-dose and post-dose fasting period of 0.5 hour to 1 hour applies. No fluid intake (including water) is allowed for 1 hour pre-dose to 1-hour post-dose).
g	Virus serology (RSV neutralisation antibody assay) will be performed to determine eligibility and seroconversion.
h	Upper respiratory tract swab (e.g., nasopharyngeal swab, mid-turbinate swab, oropharyngeal swab) for respiratory virus screen to assess for the presence of respiratory pathogens; if found positive for any pathogen in the panel, the participant will not be eligible for the current quarantine.
i	Post inoculation nasal wash virology samples will be collected at the same time each day during quarantine (± 1 hour from baseline on Day 2) and used for qRT-PCR and viral culture assay (as appropriate). Samples may be used for related viral genomics [redacted] Samples collected between the morning of Day 2 and the morning of Day 5 will also be used for qicPCR until a positive result is received (to support triggered dosing).
j	Adverse events and concomitant medications are reviewed throughout the study including pre- and post-dosing with IMP and pre- and post-RSV virus inoculation.

k	IMP doses as oral solution/suspension will be taken with 140 mL of water (50 mL water rinse of IMP bottle following administration, and 90 mL post-dose). All participants will be dosed orally, in the seated position, under fasted conditions, under the direct supervision of the investigator (or delegate), and in accordance with the randomisation schedule. Each participant will receive IMP twice daily (~12 hours interval) for 5 consecutive days, in total 10 doses, IMP dosing to start on confirmation of RSV infection. The earliest start of IMP dosing will be in the evening of Day 2 post-HVC or IMP dosing will start in the evening of Day 5, if no confirmation of RSV infection.
Note:	Parenthesis indicates the assessment may be optional, or at the PI's discretion. The PI/investigator may perform additional safety assessments as required. Where any nasal sampling time points occur together, the order of sampling will typically be (1) nasopharyngeal swab followed by (2) nasal wash.

GENOMIC, TRANSCRIPTOMIC AND PROTEOMIC SAMPLES				
Deoxyribonucleic acid (DNA)/ ribonucleic acid (RNA)/proteomic sample collection:	**Yes**	☒	**No**	☐
	Viral RNA sequencing may be performed on laboratory-confirmed positive nasal wash samples. DNA pharmacogenomics[redacted] may be explored in appropriate samples.			
Consent considerations:	Genetic consent. Nasal samples may be tested for suspected community-acquired infections. Blood and nasal samples may be used and/or retained for[redacted] purposes related to the study objectives and respiratory virus infections.			

2. Introduction

2.1. Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is a significant pathogen of the very young, the immunocompromised, and the elderly (Simões et al, 2015), in whom infections are associated with significant morbidity and mortality (Bagga et al, 2013; Fleming et al, 2015; Hall et al, 2009; Scheltema et al, 2017). It is highly infectious and is transmitted through respiratory secretions via close contact with infected individuals, through droplets, or through contaminated surfaces (Collins and Karron, 2013). RSV outbreaks and epidemics are highly predictable year by year, peaking between January and April in the Northern Hemisphere and during the Southern Hemisphere winter season. This predictability and the presence of well-established surveillance systems in many countries is useful in alerting healthcare providers and public health systems to the presence of RSV and the need for screening patients with suspected RSV infection who are at risk of disease. Accurate diagnosis and confirmation of RSV infection is now feasible due to the availability of effective point of care diagnostic assays.

In infants and small children, RSV is the major cause of lower respiratory tract infections (LRTI), manifesting as bronchiolitis or pneumonia. It has also been associated with an increased risk of recurrent wheezing and asthma. Comorbidity factors which significantly increase the risk of severe LRTI in infants include prematurity, cyanotic or complicated congenital heart disease and chronic lung disease due to prematurity. The mortality rate in the very young at-risk infants is 2 – 3 % in most developed countries. However, approximately 96% of children admitted to hospital with RSV infection are full-term and otherwise healthy. In the United States of America (USA) between 100,000 and 126,000 infants under one year of age have been hospitalised in each of the last 5 years.

In those over 60 years old, in the USA there are estimated to be more than 2 million consultations with physicians each year due to RSV infection. The virus is also a significant problem in adults with chronic obstructive pulmonary disease (COPD) where it is a major cause of exacerbations. RSV notably causes annual outbreaks of infection and disease in elderly residents of nursing homes during outbreaks.

Hospitalisation due to RSV infection is a major and significant burden on health care providers and hospitals during an RSV outbreak. Although the relationship between viral load and disease severity has not been fully established, there is growing evidence that hospitalised children with RSV disease have higher nasal viral titres than age-matched controls with less severe disease suggesting a potential opportunity to intervene with an effective antiviral agent.

Opportunities for intervention, either therapeutically or prophylactically, exist in all these populations. Studies have demonstrated that children can see up to 3 physicians prior to hospital admission presenting multiple opportunities for diagnosis and intervention. Increasing awareness of RSV infection and its consequences in the elderly and in adults with co-morbidities that put them at risk of complicated RSV disease, along with the development of rapid diagnostics, will provide opportunities to treat or prevent RSV infection and disease in these vulnerable populations. Due to the high risk of RSV in haematopoietic stem cell transplantation patients, this population is routinely monitored during RSV epidemics and early treatment to prevent significant morbidity and mortality is required.

Currently there are limited treatment options for RSV infection. There are no RSV vaccines and only 2 approved therapeutic agents. The first, Ribavirin, is a nucleoside analogue, but clinical use is restricted due to its limited antiviral potency, delivery route, toxicity, and teratogenic potential (Kim et al, 2017). The other is the prophylactic monoclonal antibody Synagis® (palivizumab), which interacts with the F-glycoprotein of the RSV virus. Palivizumab has been shown to provide protection in infants but needs to be given before infection and throughout the winter season. It is approved for use in infants with a history of prematurity, haemodynamically significant cardiac disease, or chronic lung disease of prematurity. Cost of treatment also limits its use. There is therefore an ongoing unmet medical need for an effective therapy for RSV infection and a number of new treatments targeting various mechanisms of action are in development, including inhibitors targeting RSV fusion, polymerase, and N protein as well as prophylactic agents and vaccines.

In summary, due to the current lack of availability of suitable therapeutic and prophylactic agents and vaccines against RSV and the significant unmet clinical need there is urgent need for a well-tolerated and effective anti-RSV agent. Populations that will particularly benefit from a small molecule therapeutic or prophylactic agent include infants and small children as well as adults, particularly the elderly, those with co-morbid disease such as COPD, and the immunocompromised.

2.2. RV299

RSV, a member of the Pneumovirus family, is an enveloped virus with a negative single strand ribonucleic acid (RNA) genome that encodes for 11 proteins, including 3 surface glycoproteins (F, G, and SH). After fusion, the RSV RNA enters the cell and directs the synthesis of virus proteins, including the virus polymerase (L) and N protein involved in replicating the virus RNA. The N protein is an essential component of the RSV replication machinery and coats the newly synthesised viral RNA antigenome allowing new RSV genome to be synthesised. There are 2 major RSV subtypes, A and B, that cause similar disease and although they may co-circulate, one type usually predominates in alternative years.

RV299 is an inhibitor of the RSV N protein, which is an essential component of the RSV replication machinery. Inhibitors of the N protein can prevent the replication of the virus in the host cell and thus prevent new virus particles from being formed and transmitted.

2.2.1. Summary of Pre-clinical and Clinical Experience

RV299 is a novel replication inhibitor of RSV. It is a potent inhibitor of RSV infection in *in vitro* assays and is effective against a panel of RSV laboratory and clinical isolates of RSV A and B strains. RV299 is specific for RSV with no cross-activity against other viruses tested, and the antiviral effect is not due to cytotoxicity. Following prolonged *in vitro* culture, RSV resistant to RV299 was selected; genotypic analysis and cross resistance studies suggest that the compound targets RSV nucleoprotein (N), an essential component of viral RNA-dependent RNA polymerase, which is responsible for viral replication and transcription.

Single dose absorption, distribution and metabolism studies demonstrated RV299 has good oral absorption, low clearance, and low-moderate volume of distribution, resulting in moderate exposure and high oral bioavailability. Plasma protein binding of RV299 was moderate-high in rats, dogs, and humans. *In vitro* experiments in human cytosol showed that RV299 was metabolised by aldehyde oxidase, and in human microsomes, an oxidative metabolite was observed that was not present *in vivo* in rats or dogs.

RV299 does not exhibit competitive cytochrome P450 (CYP) enzyme inhibition against any of the major CYP isoforms with the exception of CYP2C8 (50% inhibitory concentration [IC_{50}] = 5.70 µM) but at the proposed doses, is not anticipated to cause a clinical drug-drug interaction (DDI). However, as the *in vitro* assay was limited due to solubility, it cannot be discounted that there may be a possibility of CYP3A4 inhibition in the intestine. RV299 is also an inhibitor of organic anion transporter protein B, organic cation transporter 2, and bile salt export pump (IC_{50} ≤16.3 µM) but at the proposed doses it is not anticipated that this will cause a clinical DDI. RV299 did not show measurable P-glycoprotein (P-gp) or breast cancer resistance protein inhibition in the *in vitro* assay (IC_{50} >30 µM). Even though the concentration of RV299 investigated in this assay was limited due to low solubility, when an IC_{50} of 30 µM (worst case scenario) is used in predictions, this suggests that a DDI in the intestine is unlikely. RV299 caused a >2-fold increase in CYP3A4 and CYP2B6 messenger RNA (mRNA) and a >20% increase in catalytic activity compared to the respective positive controls. It is anticipated that RV299 may have the potential for enzyme induction in humans

Good Laboratory Practice (GLP)-complaint toxicity studies of up to 14 days duration have been conducted with RV299 in rats (25, 80, 250 mg/kg/day) and dogs (15, 50, 150 mg/kg/day), by once daily oral administration. The highest dose tested in rats, 250 mg/kg/day, was considered the no-observed-adverse-effect-level (NOAEL). In dogs, adverse clinical observations were noted at 150 mg/kg/day and animals assigned to a 2-week recovery period were terminated prematurely within 5 days of cessation of dosing. The principal target organs for toxicity were lymphohematopoietic tissues. Marked myelosuppression/immunodepression, including thrombocytopenia, decreases in reticulocyte and white cell counts and pronounced decreases in cellularity in bone marrow and lymphoid tissues, were noted at 50 mg/kg/day and 150 mg/kg/day. Adverse effects (inflammation and atrophy) were also noted in the gall bladder. These findings were noted where mean maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve over the last 24 hours dosing interval ($AUC_{0\text{-}24h}$) values were 4-fold greater than the mean values following a clinical dose of 65 mg twice a day (bis in die; BID).

Overall, data from *in vitro* and *in vivo* for genotoxicity studies demonstrated RV299 was not genotoxic.

RV299 had no effects on the respiratory, or central nervous systems in rats at oral doses up to 250 mg/kg, nor on the cardiovascular system of telemetered dogs at an oral dose of 50 mg/kg.

RV299 has been evaluated in a single clinical study (REVD001) in a total of 32 healthy adult subjects and a cumulative total of 136 doses spanning single doses of 25 to 125 mg and multiple doses of 35 to 65 mg BID for 9 doses. The study also included 10 subjects on matched placebo. The study is ongoing and so the data from this study is still blinded and the safety profile of RV299 has therefore been assessed in aggregate form with placebo.

The data to date suggest that RV299 has a favourable safety profile across the range of doses covered. There have been no clinically significant findings to date on any safety parameters including laboratory results, telemetry, electrocardiograms (ECGs), or vital signs. There have been no serious adverse events (SAEs), nor any moderate or severe non-SAEs. All adverse events (AEs) have been mild, self-limiting, and resolved completely. There have been no emerging trends in any safety findings either in isolation within individual cohorts or in comparison with previous cohorts. The data review committee has reviewed the data for each completed cohort to support progression to the next cohort, and in all instances has approved dose progression.

RV299 demonstrated predictable pharmacokinetics (PK) across the dose range studied. Half-life, clearance, and apparent volume of distribution values were consistent across the doses. RV299 PK after both single and multiple twice daily dosing demonstrated reasonable dose proportionality across the respective dose ranges studied. The multiple-dose data suggests that RV299 plasma PK are linear upon multiple dosing.

Geometric mean $AUC_{0\text{-}24h}$ and C_{max} on Day 5 following the 65 mg BID dose regimen provide a 4-fold margin to the respective NOAELs that have been set by the 14-day dog GLP study at a dose of 15 mg/kg/day. Even when using the maximum observed values in the 65 mg BID dose regimen, there was still a 2-fold safety margin to the respective NOAELs for $AUC_{0\text{-}24h}$ and C_{max}.

The administration of RV299 with food marginally decreased the rate of absorption and C_{max} but had no observable effect on the overall exposure indicated by $AUC_{0\text{-}\infty}$. On this basis RV299 can be administered without regard to food.

2.3. The Respiratory Syncytial Virus Human Challenge Model

The RSV human challenge model was developed to not only aid understanding of RSV disease, but to also assess the efficacy of RSV antivirals, immunomodulators and vaccines. The RSV-A Memphis 37b challenge strain has been used for over 15 years by both hVIVO and others and has helped assess the efficacy of numerous RSV therapies (as reviewed by Lambkin-Williams et al, 2018; DeVincenzo et al, 2020a; DeVincenzo et al, 2020b; Stevens et al, 2018) and vaccines (Sadof et al, 2021; Pfizer 2021; Bavarian Nordic 2021). Specifically, hVIVO have safely and successfully used the RSV challenge strain in over 1400 healthy participants (18 to 60 years of age) including the inoculation of 24 participants between 60 and 75 years of age. Additionally, another clone of the same strain of live RSV (Memphis 37c) has been used as an inoculation agent and was shown to be safe in over 77 healthy young adults across 3 studies. Healthy RSV challenge study participants have approximately 65% to 85% chance of becoming infected with RSV following the administration of the virus (DeVincenzo et al, 2010). Typical RSV illness is characterised by an abrupt onset of rhinitis, nasal stuffiness, malaise, myalgia (muscle aches), and sore throat. In healthy adults, the illness usually resolves without any treatment, with relief of symptoms occurring naturally within 7 to 10 days. Respiratory syncytial virus, like many viruses, can cause more substantial health issues such as myocarditis (inflammation or damage to the heart muscle). Adults and children present with RSV-related myocarditis rarely, with symptomless occurrences likely going undiagnosed in the community.

2.4. Study Rationale

Collectively, the clear unmet medical need for an effective therapy for RSV infection and the RV299 pre-clinical pharmacology and toxicology profile provide strong rationale for its clinical development. The rationale for taking RV299 into further development is the expectation that this compound could be effective for the treatment of RSV. Prior to initial testing in the primary target populations (typically the immunocompromised, young children and elderly people), the safety, tolerability, antiviral activity, and the PK characteristics of the drug in healthy adults will be investigated.

The purpose of this study is to confirm the antiviral activity of RV299 in a population inoculated with RSV-A Memphis 37b challenge strain.

The RSV-A Memphis 37b challenge strain has been used for over 15 years by both hVIVO and others and has helped assess the efficacy of numerous RSV therapies. Specifically, hVIVO have safely and successfully used the RSV challenge strain in over 1400 healthy participants (18 to 60 years of age) including the inoculation of 24 participants between 60 and 75 years of age.

2.5. Benefit/Risk Assessment

2.5.1. Risk Assessment

The known risks to participants are detailed in Table 2-1. 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.

There is currently limited clinical experience with RV299. More detailed information about the known and expected benefits and risks and reasonably expected AEs of RV299 may be found in the Investigator's Brochure.

Table 2-1: Risk Assessment

Potential Risk of Clinical Significance	Description of Risk	Mitigation Strategy
Study Intervention		
Oral dosing with RV299	1) RV299 has not previously been tested in human subjects infected with RSV and may not confer any antiviral protection against RSV in humans despite encouraging pre-clinical evidence. 2) Pre-clinical studies have identified myelosuppressive effects (including reduced reticulocytes, platelets and white cell counts and fractions) in dogs following 14 days' administration at doses well in excess of the intended human dose (50mg/kg/day). No such effects were seen at 15mg/kg/day and this dose was used to set the NOAEL for human administration of RV299. 3) RV299 has shown variable PK with some subjects experiencing higher exposures (doubling) for a given dose than other subjects, possibly due to differences in clearance.	1) Subjects will be monitored for severe RSV-related disease throughout the study and managed accordingly with supportive measures and may be withdrawn from the study at the investigator's discretion at any time. 2) The 65mg dose has been administrated to healthy human volunteers twice daily for 5 days and there has been no evidence of myelosuppressive effects during dosing or during the 3-week follow-up period after the last dose. The same study confirmed that the 65mg dose produces PK exposures in humans that are 2- to 4-fold below the NOAEL, providing an adequate safety margin. Subjects in the viral challenge study will have safety bloods assessed throughout the dosing interval and during follow-up to continue to monitor for any myelosuppressive effects. 3) The dose has been selected to ensure that the NOAEL safety margin is not exceeded even in subjects who may experience doubling in RV299 exposure for a given dose.
Oral dosing with placebo	Given that the placebo is a pharmacologically inert material, there should be no risk.	Not applicable.
Pregnancy and birth control	No reproductive system studies have been conducted with RV299 to date. Drugs or other substances known to be substrates for CYP3A4 or inhibitors of aldehyde oxidase (AO), P-gp) or breast cancer resistance protein (BCRP) may interact with RV299, which has shown *in vitro* evidence of being a CYP3A4 inhibitor and an AO, PgP, and BCRP substrate. Caution should be applied in co-administering such therapies, including monitoring for toxicity or subtherapeutic effects.	1) Specific contraceptive requirements will be in place for participants. 2) Contraceptive guidance will be used in inclusion criteria. 3) Female participants will need evidence of negative pregnancy tests prior to dosing.

Potential Risk of Clinical Significance	Description of Risk	Mitigation Strategy
	In particular, female participants who are on hormonal contraception or hormonal replacement therapy that contains oestradiol or ethinyl-oestradiol (both of which are substrates of CYP3A4) should require their male partners to use additional barrier contraceptive methods such as condoms with spermicide during RV299 administration and for at least one menstrual cycle after a course of RV299.	
Study procedures		
Blood Sampling (venepuncture or via a peripheral venous catheter)	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.
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 to minimise the discomfort
RSV infection from inoculation		
RSV infection & severe complications	65% to 85% chance of becoming infected with RSV-A Memphis 37b. Typical RSV illness: abrupt onset of rhinitis, nasal stuffiness, fever, malaise, myalgia (muscle aches), and sore throat.	The safety profile of the RSV-A Memphis 37b is well characterised in healthy adults as this has been used for over 15 years by hVIVO. At hVIVO more than 1400 healthy adults aged 18 to 60 years have been challenged with the RSV challenge strain.

Potential Risk of Clinical Significance	Description of Risk	Mitigation Strategy
	Severe RSV infections are known to occur in both infants and adults. In adult populations, multiple factors but not older age, are independently associated with severe RSV complications including persons of any age with chronic co-morbidities and significant immune compromise. RSV, like many viruses, can cause more substantial health issues such as myocarditis (inflammation or damage to the heart muscle). Adults and children present with RSV-related myocarditis rarely, with symptomless occurrences likely going undiagnosed in the community. Within our RSV viral challenge studies, of over 1400 participants who have received the challenge virus to date, the occurrence of myocarditis is uncommon. None of these participants reported any symptoms due to myocarditis and, where follow-up was completed, the diagnostic tests related to the follow-up returned to normal without treatment.	RSV infection in healthy adults usually resolves without treatment within 7 to 10 days. 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 12 days post human viral challenge (HVC). Qualified medical and nursing staff in the quarantine unit will monitor for and manage any symptoms. Participants will be closely followed up while being in quarantine. Electrocardiograms will be performed, and cardiac enzymes will be tested at least 7 days and 11 days post-viral challenge.
	Transient increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) without clinical presentation, with a good prognosis upon improvement of infection.	ALT and AST will be monitored.
Transmission of RSV to participants' close contacts	RSV 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. This is based on experience to date with more than 1400 inoculations, As appropriate, the PI/delegate may request additional testing of nasal swab samples using a qualitative virus antigen test or PCR to assist in determining participants' suitability for departure. As an additional precaution, participants will be instructed to avoid close contact with vulnerable individuals as described in

Potential Risk of Clinical Significance	Description of Risk	Mitigation Strategy
		Section 2.5.1.1, Vulnerable Persons, for 2 weeks after they leave the quarantine unit.
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.		

2.5.1.1. 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, COPD).
    - 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).

2.5.1.2. Risk Associated with Coronavirus Disease 2019 Pandemic

hVIVO has implemented enhanced infection control measures during the pandemic to minimise risks of 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 RSV-A Memphis 37b.

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 RV299 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.

2.5.2. Benefit Assessment

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

Participants may develop some immunity to RSV-A Memphis 37b 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.

2.5.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimise risk to participants in this study, the potential risks identified in association with RSV virus infection and RV299 treatment are justified by the anticipated benefits linked to the evaluation of the antiviral activity of RV299 in the viral challenge model which will contribute to the development of a new therapy for the treatment of RSV infection.

3. Objectives and Endpoints

Objectives	Endpoints
Primary:	
Efficacy	
• To assess the antiviral activity of RV299 compared to placebo in healthy adult participants infected with RSV-A Memphis 37b.	• The area under the curve (AUC) for RSV viral load measured in nasal washes by quantitative real time reverse transcription polymerase chain reaction (qRT-PCR) in participants inoculated with RSV-A Memphis 37b, starting at initial administration of investigational medicinal product (IMP) up to planned discharge from quarantine (Day 12, am).
Secondary:	
Efficacy	
• To evaluate the effect of RV299 compared to placebo in healthy adult participants inoculated with RSV in terms of antiviral effect assessed by: o Viral-load related endpoints.	Additional viral load endpoints relating to antiviral effect include, but are not limited to: • Peak viral load of RSV as defined by the maximum viral load determined by qRT-PCR measurements in nasal samples starting from initial administration of IMP up to planned discharge from quarantine (Day 12, am). • Time (days) to confirmed negative test by qRT-PCR measurements in nasal samples starting at initial administration of IMP to first confirmed undetectable assessment after peak measure. • Time (days) to confirmed negative test by qRT-PCR measurements in nasal samples starting from peak qRT-PCR after initial administration of IMP to first confirmed undetectable assessment after peak measure. • Time (days) to peak qRT-PCR in nasal samples, starting from initial administration of IMP. • Area under the viral load-time curve (VL-AUC) of RSV challenge virus as determined by viral culture on nasal samples, starting at initial administration

Objectives	Endpoints
	of IMP up to planned discharge from quarantine (Day 12, am). • Peak viral load of RSV as defined by the maximum viral load determined by viral culture measurements in nasal samples starting from initial administration of IMP up to planned discharge from quarantine (Day 12, am). • Time (days) to confirmed negative test by viral culture measurements in nasal samples starting at initial administration of IMP to first confirmed undetectable assessment after peak measure. • Time (days) to confirmed negative test by viral culture measurements in nasal samples starting from peak viral culture after initial administration of IMP to first confirmed undetectable assessment after peak measure.
• To evaluate the effect of RV299 compared to placebo in healthy adult participants inoculated with RSV in terms of antiviral effect assessed by: ○ Clinical symptom-related endpoints.	Clinical symptom-related endpoints include, but are not limited to: • Area under the curve over time of total clinical symptoms (TSS-AUC) as measured from 10 symptoms within the graded symptom scoring system collected 3 times daily starting at initial administration of IMP up to planned discharge from quarantine (Day 12, am). • Area under the curve over time of total clinical symptoms change from baseline (TSS-AUC-CFB) as measured from 10 symptoms within the graded symptom scoring system collected 3 times daily starting at initial administration of IMP up to planned discharge from quarantine (Day 12, am). • Peak symptoms diary card score: peak total clinical symptoms (TSS) as measured from 10 symptoms within the graded symptom scoring system collected 3 times daily starting from initial administration of IMP up to planned discharge from quarantine (Day 12, am). • Peak daily symptom score: individual maximum daily sum of symptom score from initial

Objectives	Endpoints
	administration of IMP up to planned discharge from quarantine (Day 12, am). • Time (days) to symptom resolution as measured from 10 symptoms within the graded daily symptom scoring system starting at initial administration of IMP to time of returning to baseline score. • Time (days) to symptom resolution as measured from 10 symptoms within the graded daily symptom scoring system starting at peak symptoms after initial administration of IMP to time of returning to baseline score. • Time (days) to peak as measured from 10 symptoms within the graded daily symptom scoring system starting from initial administration of IMP to the time of peak daily symptom score.
• To evaluate the effect of RV299 on nasal discharge in healthy adult participants inoculated with RSV when compared to placebo.	• Total weight of mucus produced starting at initial administration of IMP up to planned discharge from quarantine (Day 12, am). • Total number of tissues used by participants starting at initial administration of IMP up to planned discharge from quarantine (Day 12, am).
Safety	
• To evaluate the safety of multiple orally administered doses of RV299 when compared to placebo.	• Safety data including, but not limited to, occurrence of AEs from initial administration of IMP up to the Day 28 follow-up. • Occurrence of SAEs from initial administration of IMP up to the Day 28 follow-up.
• To monitor the safety of the challenge virus.	• Occurrence of AEs related to the viral challenge from viral challenge (Day 0) up to the Day 28 follow-up. • Occurrence of SAEs related to the viral challenge from viral challenge (Day 0) up to the Day 28 follow-up. • Use of concomitant medications from viral challenge (Day 0) up to the Day 28 follow-up.

Objectives	Endpoints
Pharmacokinetics	
• To characterise the PK profile of RV299 after a single oral dose and after multiple oral doses in plasma from healthy participants inoculated with RSV.	Secondary endpoints related to PK include, but are not limited to: • Time to maximum plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), C_{max}, area under the plasma concentration-time curve from time zero to the end of the dosing interval ($AUC\tau$), AUC_{0-24h}, and area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$).
CCI [redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

*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 from 18 to 55 years of age, inclusive, utilising:

- IMP (active): RV299cci [redacted] dosed twice daily (~12 hours interval) for 5 consecutive days (a total of 10 doses)
- IMP (placebo): Placebo to Match RV299cci [redacted] dosed twice daily (~12 hours interval) for 5 consecutive days (a total of 10 doses)
- Challenge agent: RSV-A Memphis 37b, intranasally administered

The primary goal of this Phase 1b study is to assess the antiviral activity of RV299 against RSV in the viral challenge model. In addition, the safety, tolerability, and PK of RV299 will be assessed.

A total of 80 participants is planned to be enrolled in this study: 40 participants on RV299 and 40 participants on placebo.

The expected duration of study participation for a participant is 1 month (screening not included), with the following sequence and duration of study phases:

- **Screening phase**: from Day -90 to Day-3 pre-HVC. 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 15 days (from Day -2 to Day 12). Procedures will include:
  - **Pre-HVC**:
    - Admission to quarantine unit on Day -2/-1.
    - Baseline assessments will be conducted as per Schedule of Events (SoE) up to Day 0, pre-challenge.
  - **HVC**:
    - RSV-A Memphis 37b virus inoculation on Day 0.
  - **Post-HVC**:
    - Randomisation to receive RV299 or matched placebo.
    - Administration of IMP (RV299/placebo). Each participant will receive IMP twice daily (~12 hours interval) for 5 consecutive days:
      - IMP dosing to start on confirmation of RSV infection, i.e., after a positive result by qualitative integrative cycler polymerase chain reaction (qicPCR). The qicPCR of nasal wash will be performed twice daily on Days 2-5 (Day 5 morning only), or until a positive result is received, whichever is sooner. The earliest start of IMP dosing will be in the evening of

Day 2 post-HVC (IMP will be initiated 12 hours ± 1-hour post nasal wash confirmation of infection)

OR

- IMP would start in the evening of Day 5, if no positive result obtained by qicPCR

- Day 1 onwards and each day – study assessments will be conducted as per SoE.
- Participants will be discharged from the quarantine unit on Day 12 (or may remain longer at the discretion of the principal investigator [PI]/investigator).

- **Outpatient phase:**
  - Final visit: Day 28 (±3 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 RSV challenge studies. Numerous studies have been performed using experimental RSV infection in human participants. To date, in hVIVO's studies, over 1400 participants have been successfully and safely inoculated with RSV-A Memphis 37b. These studies demonstrated that adults could be infected by nasal inoculation and that experimental infection was safe. This RSV strain has been shown to cause symptoms and virus shedding that closely match natural infection.

Administration of IMP and challenge with RSV-A Memphis 37b 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

The placebo control 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 RV299.

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

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

4.3. Justification for Dose

The dose of RV299 for this study will be 65 mg twice daily for 5 days. The rationale for this dose selection is based on 3 key elements:

1. PK modelling that predicts that the human exposures achieved with the 65 mg dose given twice daily for 5 days will exceed 4 times the *in vitro* 90% effective concentration (EC_{90}) for RSV for the

full duration of therapy following the first dose and for at least 24 hours after the last dose, based on the PK data generated from the multiple-ascending dose study in humans.

2. The 65 mg dose given twice daily for 5 days provides a 2- to 4-fold margin of safety for C_{max} and $AUC_{0\text{-}24h}$ below the NOAEL set by the 14-day dog GLP study in which myelosuppressive effects were observed at 50 mg/kg/day but not at 15 mg/kg/day.
3. The first study in humans included a cohort of healthy volunteers who were randomised to receive 65 mg twice daily for 9 doses (n=6) or matched placebo (n=2), and the dosing regimen was shown to be well tolerated with a favourable safety profile. There were no SAEs or withdrawals. There were only 5 AEs reported (back pain, gastritis, incidental coryzal illness, bowel movement irregularity and headache) and all were assessed as mild and resolved completely; none were assessed as possibly or likely related to RV299. Safety blood analysis showed no clinically concerning changes, and in particular there were no changes in any haematology markers during therapy or during the 3-week follow-up period to suggest any evidence of myelosuppressive effect.

An inoculum titre of approximately 4 $\log_{10}$ plaque-forming units (PFU) of the RSV-A Memphis 37b 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. Rationale for Trial Endpoints

The measures for evaluation of the safety and tolerability profile of oral RV299 administration are standard for most clinical studies and follow the recommendations in the International Council for Harmonisation (ICH) guidelines.

The measures for evaluation of the antiviral activity of RV299 against RSV have been employed in previous studies conducted by hVIVO and are appropriate to characterise the efficacy of RV299, considering the RV299 mode of action.

The assessments for determining RV299 plasma concentrations are appropriate to characterise the PK profile of RV299.

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4.5. Population to be Studied

Healthy participants

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 visit 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 visit 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 APPROVED STANDARD INCLUSION CRITERIA** **(Viral Challenge Volunteer Studies)** Final v11.0, 08FEB2022
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 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), ECG, and routine laboratory tests as determined by the 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. Post-menopausal females defined as amenorrhea for ≥12 months with no alternative medical cause. A high follicle-stimulating hormone (FSH) level, within appropriate post-menopausal range, may be used to confirm post-menopausal 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).

No.	**hVIVO APPROVED STANDARD INCLUSION CRITERIA** **(Viral Challenge Volunteer Studies)** Final v11.0, 08FEB2022
7.	The following criteria apply to female and male participants: a) Female participants of **childbearing potential** must use **one form** of highly effective contraception. Hormonal methods must be in place from at least 14 days prior to the first study visit. The contraception use must continue until 90 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 14 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 trial 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 90 days after the last dose of IMP.

No.	**hVIVO APPROVED STANDARD INCLUSION CRITERIA** **(Viral Challenge Volunteer Studies)** Final v11.0, 08FEB2022
	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. 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 have agreed not to donate sperm following discharge from quarantine until 90 days after the last dose of IMP.
8.	Sero-suitable for the challenge virus • The serology result obtained from the RSV-A Memphis 37b virus antibody assay suggests that the participant is sensitive to RSV-A Memphis 37b virus infection (i.e., they are likely to be infected following inoculation with the challenge virus).

5.2. Exclusion Criteria

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

NO	**hVIVO APPROVED STANDARD EXCLUSION CRITERIA** **(Viral Challenge Volunteer Studies)** Final v11.0, 08FEB2022
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 or lower respiratory tract 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, immunological (including immunosuppression), metabolic, urological, renal, neurological, or psychiatric disease and/or other major disease that, in the opinion of the 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 one 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.

NO	hVIVO APPROVED STANDARD EXCLUSION CRITERIA (Viral Challenge Volunteer Studies) Final v11.0, 08FEB2022
	e) Participants reporting concurrent physician-diagnosed migraine at screening or a history of migraine likely be active at the time of inclusion into the study, is an exclusion. 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).
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 viral challenge.
5.	Lifetime history of anaphylaxis and/or a lifetime history of severe allergic reaction. 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.

NO	**hVIVO APPROVED STANDARD EXCLUSION CRITERIA** **(Viral Challenge Volunteer Studies)** Final v11.0, 08FEB2022
Prior or Concomitant Medications and Assessments	
8.	a) Evidence of vaccinations within the 4 weeks prior to the planned date of viral challenge. 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
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 date of viral challenge 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 viral challenge. b) Receipt of 3 or more investigational drugs within the previous 12 months prior to the planned date of viral challenge. 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 Viral Challenge. b) Chronically used medications, vitamins, or dietary supplements, including any medications (including St John's wort) known to be potent inducers or inhibitors of CYP enzymes, within 21 days prior to the planned date of Viral Challenge. c) Over-the-counter medications (e.g., paracetamol or ibuprofen) where the dose taken over the preceding 7 days prior to the planned date of viral challenge has exceeded the maximum permissible 24-hour dose (e.g., ≥4 grams paracetamol over the preceding week).

NO	hVIVO APPROVED STANDARD EXCLUSION CRITERIA (Viral Challenge Volunteer Studies) Final v11.0, 08FEB2022
	d) Systemic antiviral administration within 4 weeks of viral challenge.
12.	a) Confirmed positive test for drugs of abuse and cotinine on first study visit. One repeat test is allowed at PI discretion. b) 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%.
14.	Positive HIV, hepatitis B virus, or hepatitis C virus test.
15.	Presence of fever, defined as participant presenting with a temperature reading of ≥37.9°C on Day -2, Day -1, and/or pre-challenge on Day 0.
Other	
16.	Those employed or immediate relatives of those employed at hVIVO or the sponsor.
17.	Any other medical, psychiatric, social, or occupational condition and/or responsibility that, in the opinion of the investigator, would interfere with or serve as a contraindication to protocol adherence or the assessment of safety, will deem the participant unsuitable for the study. Any other reason that in the opinion of the investigator raises a concern that the subject will not be able to cope with quarantine requirements.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

All participants will be dosed under fasted conditions.

For all doses, a pre- and post-dose fasting period of 0.5 hour to 1 hour applies. No fluid intake (including water) is allowed for 1 hour pre-dose to 1 hour post-dose.

Refrain from consumption of red wine, Seville oranges, grapefruit, or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of study intervention until after the final dose.

Participants must not consume any food containing poppy seeds or any codeine-containing formulation starting 72 hours before any study visit and before admission to the quarantine unit (in order to avoid false-positive urine drug screen).

5.3.2. Caffeine, Alcohol, and Tobacco

Participants must abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours prior to and during quarantine and for 48 hours prior to all visits requiring spirometry.

Participants must not consume alcohol for 72 hours prior to and during quarantine and for 72 hours prior to any clinic visits.

Participants must not smoke or use tobacco or nicotine containing products for 72 hours prior to and during quarantine. Participants that are current smokers may be enrolled in the study if, in the opinion of the PI/investigator, cessation of smoking during quarantine will not lead to withdrawal symptoms which could interfere with the accurate recording on the symptom diary card.

5.3.3. Activity

Participants must refrain from strenuous exercise for 48 hours prior to and during quarantine and for at least 48 hours prior to each clinic visit (unless it is within the usual activity of the participant) and participants are advised to avoid any new strenuous activities for 1 week prior to clinic visits such as weightlifting or running to avoid potential spurious elevation of clinical laboratory safety parameters.

5.4. Screen Failures

Screen failures are defined as participants who sign the study-specific informed consent form (ICF) but are not subsequently enrolled into the study on that occasion. Screen failures may be invited back for repeat assessments and screening and if eligible, for study enrolment.

For individuals who do not meet the criteria for participation in this study (screen failure), the PI/investigator will decide whether the participant should be permanently excluded from the study or invited back for repeat assessments (i.e., repeat clinical laboratory test) if the initial screening assessments are still within the allowed screening windows or rescreening for a later quarantine, as appropriate.

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	IMP (Active)	IMP (Placebo)	RSV-A Memphis 37b
Type	Drug	Placebo	Virus
Dose Formulation	RV299 CCI	Placebo to match RV299CCI	Capped vial, Liquid
Unit Dose Strength(s)	65 mg as RV299 (i.e., ~130 mg as RV299CCI	Placebo to Match RV299 CCI	The challenge agent titre is determined in an infectivity assay. The dose is approximately 4 $\log_{10}$ PFU
Dosage Level(s)	65 mg as RV299 (i.e., ~130 mg as RV299CCI dosed twice daily (~12 hours interval) for 5 consecutive days (a total of 10 doses)	CCI dosed twice daily (~12 hours interval) for 5 consecutive days (a total of 10 doses)	A single dose of challenge agent will be delivered
Route of Administration	Oral	Oral	Intranasal
Use	Experimental	Other/placebo	Infectious challenge agent
Sourcing	Provided by ReViral Limited	Commercially available	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	RSV challenge agent will be provided in vials. The details of the challenge agent provision will be provided in the analytical plan
Current/Former Name(s) or Alias(es)	Not applicable	Not applicable	Not applicable

6.2. Preparation/Handling/Storage/Accountability/Administration

6.2.1. Investigational Medicinal Product

hVIVO will receive supplies of Qualified Person-certified IMP (measured doses RV299CCI [redacted] after it has been authorised for shipment by the sponsor from the Manufacturing and Import Authorisation (IMP) licensed Good Manufacturing Practice (GMP) facility. All IMP supplies to hVIVO will be used only for this protocol and for no other purpose.

IMP will be supplied throughout the study. Once received at hVIVO, hVIVO study staff will perform stock level accountability and the IMP will be stored securely, according to the storage conditions described on the IMP labels. IMP 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 temperature of the storage location of the IMP is monitored. Accurate records will be kept of when and how much IMP 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.

Prior to dosing RV299 CCI [redacted] RV299CCI [redacted] or placebo doses will be taken with 140 mL of water (50 mL water rinse of RV299/placebo bottle following administration, and 90 mL post-dose). All participants will be dosed orally, in the seated position, under fasted conditions, and under the direct supervision of the investigator (or delegate), and in accordance with the randomisation schedule.

6.2.2. Challenge Agent

The challenge agent used in this study is RSV-A Memphis 37b.

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 -80°C freezer (normal temperature range[redacted]

Inoculum vials containing the challenge agent will be used for intranasal inoculation of each participant. The inoculum will be prepared and/or provided according to the hVIVO analytical plan (AP) and administered in accordance with hVIVO standard operating procedures (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 specifically for potential allergic reactions and any AEs for the following 24 hours. Post inoculation, participants will lie flat for 10 min then sit up with nose pegs on for 20 min. Participants will continue to be monitored throughout the clinical phase of the study.

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 IMP are provided in the pharmacy manual.

6.3. Randomisation and Blinding

hVIVO assigns a unique 6-digit number to each participant in the hVIVO database. This number will be used to identify a participant up to the point of randomisation, on source documents, on all study correspondence and in the study database. A separate randomisation number will be allocated to the

participants at randomisation and will be used for allocation to a study arm. The randomisation number encodes the participant's assignment to 1 of 2 study arms (RV299/placebo) in a 1:1 ratio.

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 **3**-digit format e.g., **[001]**. 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 100. 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/designee preparing the IMP, so that IMP can be prepared for each participant as appropriate. An independent statistician prepares the randomisation schedule, and 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, labelled with his/her unique randomisation number, throughout the study. With the exception of the unblinded pharmacist, unblinded IMP management personnel at the clinical site, the unblinded statistician preparing the randomisation code list, and the quality assurance auditors where necessary, the PI/investigator and all other clinical and nonclinical staff, (including the study statistician, 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.

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.

The PI/investigator will be provided with a tamper-evident sealed envelope containing details of the treatment for each participant. All opened and unopened envelopes will be collected or destroyed after the end of the study, as agreed with the sponsor.

Individual emergency code break envelopes will be provided to the PI/investigator should it be necessary to break the blind for a participant. The PI/investigator will ensure there is an appropriate procedure in place to allow access to the code break envelopes in case of an emergency arising during the quarantine period, as per hVIVO's SOPs. An emergency means that the relevant medical decision on the further care of a participant is dependent on the actual identity of the study treatment that the participant has received.

The emergency code break envelopes will contain details of the treatment for each participant.

When the code break envelope is opened, the PI/investigator must note the date, time, reason for unblinding and the details of the PI/investigator and or designated site staff that broke the blind and record this information according to hVIVO SOPs. The PI/investigator must also immediately notify the sponsor's medical monitor that the code has been broken. If possible, the sponsor should be consulted before the code is broken, but this will only occur if the safety of the participant will not be compromised.

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.

Dosing with IMP must be discontinued after unblinding, but the participant will be followed up until resolution of any AEs.

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 final study contact Day 28 (±3 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 viral challenge 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.	4 weeks prior to first study visit.
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.	7 days prior to the planned date of viral challenge: • Herbal supplements • Any medication or product (prescription or over-the-counter) for symptoms of nasal congestion • Short and long-acting antihistamines

Prohibited medication	Washout
	Within 21 days prior to the planned date of viral challenge: • Chronically used medications, vitamins, or dietary supplements, including any medication known to be moderate/potent inducers or inhibitors of cytochrome P450 enzyme
Any IMP used in another study.	Within 3 months or 5 half-lives of the IMP used in the other study, whichever is greater, prior to the planned date of viral challenge.

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.

The use of paracetamol and/or other allowed medications is permissible up to 7 days before the planned date of viral challenge. During the study, the PI/investigator may permit a limited amount of paracetamol (no more than 4 g per day, i.e., maximum daily dose) or topical medication, as clinically required for the treatment of headache or any other pain. Other medication to treat AEs may be prescribed if required.

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

Table 6-3: Permitted Medication

Permitted medication	Time period
Paracetamol	Maximum 4 g daily throughout the study duration at the discretion of the PI/investigator.
Oral 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

This is not applicable in this study.

6.7. Treatment of Overdose

For this study, any dose of study 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 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. Obtain a plasma sample for PK analysis approximately 4 hours after study drug administration.
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

The sponsor is responsible for notifying the MHRA and Research Ethics Committee (REC) of the potential 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.

The sponsor 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.

Participants will be counselled that early withdrawal from the HVC phase of the study is strongly discouraged, as it may pose a risk both to the participant and his/her contacts. In the event of a participant insisting on early withdrawal during the quarantine isolation period, the participant will be encouraged to stay and would be advised of the potential risks of carrying RSV infection into the community, and to vulnerable groups in particular as described in Section 2.5.1.1, Vulnerable Persons.

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

Enrolled participants will be discontinued from study drug receipt for any of the reasons listed below. These participants must not receive any additional 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 (if pregnancy is specified as an exclusion criterion).

Enrolled 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

If a participant is found to be ineligible due to transient circumstances (such as acute disease and/or fever) at the quarantine admission, inoculation with challenge agent will be postponed until the transient circumstances have been resolved and the participant may be re-invited to a later quarantine group within the allowed time window. For participant rescreening refer to Section 5.4, Screen Failures.

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.

If a participant discontinues from study intervention OR withdraws from the study for reasons not related to AEs, a replacement participant may be enrolled if deemed appropriate by the investigator and sponsor. The replacement participant will generally receive the same intervention as the participant being replaced. The replacement participant will be assigned a unique treatment/randomisation number equalling the randomisation number of the replaced participant, plus 100. This will ensure that the replacement participant receives the same allocated, blinded treatment as the participant who is being replaced.

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.

Three clinical scenarios relating to the incidence of SAEs/suspected unexpected 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 report has been received of one (or more) SUSAR(s) in any, one (or more) participant(s).	If such a status occurs at any point during the study, then further administration of the IMP 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 (approval of a substantial amendment from the Competent Authorities is required) or terminate the study.
2	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, but which collectively represent a concern for safety.	If such a status occurs at any point during the study, then further administration of IMP 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 (approval of a substantial amendment from the Competent Authorities is required) or terminate the study.
3	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 28 (±3 days). Follow-up of any event should continue until resolution, stabilisation, it is judged by the PI/investigator to be no longer clinically significant, the participant is lost to follow-up, or an alternative explanation has been provided.

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 a non-substantial 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. Any study cohort may run at the same time	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 trial due to the meeting of stopping rules. 2. Replacement participants will be given replacement randomisation numbers (see Section 7.4, Participant Replacement Strategy). 3. 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. 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.	1. The maximum blood volume will not be exceeded. 2. Any required additional safety assessments, or specialist referrals, will be conducted on a 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 (as detailed in this protocol), and the participant's

Adaptive Design Category	Feature	Limit
		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		
Participants	Not applicable	-
Dosing	Not applicable	-

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.

Procedures conducted as part of the hVIVO generic screening process and obtained before signing of the study-specific ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoE.

The maximum volume of blood collected from each participant over the duration of the study (i.e., from screening through final follow-up visit) will not exceed 550 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. If additional samples are required in excess of this amount, e.g., to monitor laboratory abnormalities, these will be taken at the discretion of the PI/investigator.

Where applicable, unless otherwise stated, normal ranges will be identified 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: $BMI\ (kg/m^2) = \frac{\text{Body Weight (kg)}}{\text{Height (m)}^2}$

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 and/or generic screening analytical plan.

Serum levels of pre-existing RSV-A Memphis 37b-specific antibodies will be determined using RSV challenge virus neutralisation assay, as described in the AP.

8.1.5. Patient Health Questionnaire and Generalised Anxiety Disorder Questionnaire

PHQ-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.

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8.2.3. Viral Shedding for Dosing

Viral shedding will be confirmed by qicPCR assay of nasal wash samples.

8.2.4. Viral Sequencing

Laboratory-confirmed positive nasal wash samples may be analysed for resistance mutations.

Resistance monitoring will be conducted by sequencing or other appropriate methodology of the challenge agent to monitor for treatment-emergent resistance mutations. The nasal wash sample will be sent to a sponsor-designated laboratory (or hVIVO where applicable) for analysis in accordance with the AP.

8.3. Efficacy Assessments

8.3.1. Viral Shedding Assessment

Viral titre will be determined by qRT-PCR and a viral culture assay (as appropriate) 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.

Previous studies with RSV-A Memphis 37b have used a 10-item symptom questionnaire. The 10 symptoms out of the 13 listed above will be used for the primary analysis, and excludes the following 3 symptoms that may be additionally explored separately:

- Chilliness/feverishness
- Chest tightness
- Wheeze

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, collection of paper tissues will occur at the same time each day (±1 hour) with tissues distributed 24 hours ahead.

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

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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 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.

Assessment and grading of any upper respiratory tract (URT) (nasal discharge, otitis, pharyngitis, sinus tenderness) and lower respiratory tract (LRT) symptoms (abnormal breath sounds externally [e.g., stridor, wheezing] and on chest auscultation [rhonchi, crepitations, or other]) will be performed, as applicable. Physician-reported assessments of challenge agent-related illness will be graded in accordance with its intensity and documented in the source data.

Following challenge agent inoculation, additional symptoms that are not available in the list of symptoms of the symptom diary card and are deemed to be clinically significant (in the opinion of the PI/investigator) will be captured as AEs (for more details see Section 10.3.6.2, Assessment).

Following challenge agent inoculation all unexpected (in the opinion of the PI/investigator) symptom-directed physical examination findings will be captured as AEs, along with all other occurrences that meet the criteria for an AE.

8.4.3. Vital Signs and Tympanic Temperature

Vital signs assessments will be recorded as follows:

- Heart rate (HR) will be recorded in beats per minute.
- Respiratory rate (RR): respirations will be counted and recorded as breaths per minute.

- Blood pressure (BP): systolic BP and diastolic BP will be measured in millimetres of mercury (mmHg); measurements will be made supine. Where possible, the same arm will be used for all measurements.
- Peripheral arterial oxygen saturation (SpO_2%) will be assessed using pulse oximetry.
- Tympanic temperature will be measured.

If a participant has an unexpected abnormal or out-of-normal-range result, the assessment may be repeated after at least 2 minutes to exclude a technical fault and confirm the original result. The assessment may then be repeated at the discretion of the PI/investigator and in accordance with hVIVO SOPs.

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 Common Terminology Criteria for Adverse Events (CTCAE) grading table November 2017.

Deterioration in a vital sign (compared to baseline) should only be reported as an AE if the deterioration fulfils the criteria for an AE. If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated vital sign will be considered as additional information.

Temperature may be monitored more frequently during quarantine, if appropriate.

Following challenge agent inoculation, pyrexia (temperature ≥37.9°C) will be expected and presumed to represent infection consequent to viral challenge and will not be additionally captured as an AE unless it meets the definition of an AE and is deemed to be clinically significant (in the opinion of the PI/investigator) to be classed as an AE.

Following challenge agent inoculation, all unexpected (in the opinion of the PI/investigator) pyrexia will be captured as an AE, along with all other occurrences that meet the criteria for an AE.

8.4.4. Electrocardiogram

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

Twelve-lead ECGs will be obtained to evaluate the electrical activity of the heart. Electrocardiograms will be read on-site by an appropriately qualified physician or a member or the investigator site staff. Wherever possible the same qualified physician or a member or the investigator site staff will review subsequent ECGs from the same participant for the assessment of any change from baseline.

Any changes from baseline during the study will be assessed for their clinical significance. Clinically significant changes will be reported as AEs. The PI/investigator or delegate will assess nonclinical significant changes to determine whether they should be recorded.

8.4.5. Clinical Safety Laboratory Assessments

8.4.5.1. 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.

If the dipstick yields potentially clinically significant abnormal results, a urine sample may be sent for microscopy, culture, and sensitivity examination, at the discretion of the PI/investigator. Microscopy, culture, and sensitivity examination will include but is not limited to red blood cells, white blood cells, epithelial cells, crystals, casts, and bacteria.

Urine safety analysis values will be evaluated by the PI/investigator for clinical relevance. Those values that meet the criteria for an AE and are deemed to be clinically significant, will be reported as AEs.

8.4.5.2. Drugs of Misuse and Cotinine

Urinalysis will be performed for drugs of abuse and cotinine using commercially available kits that provide an instant result, which will be documented in the source data.

Drugs of abuse screen will include (but is not limited to) amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines.

8.4.5.3. Alcohol Breath Testing

Alcohol breath testing will be conducted to determine compliance with the study alcohol restrictions. Additional tests may be conducted for assessing eligibility at the discretion of the PI/investigator. Results will be recorded in the source documents.

8.4.5.4. 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, serology (HIV, hepatitis), thyroid function test, and cardiac enzymes. Additional safety assessments (e.g., coagulation) will be conducted at the discretion of the PI/investigator, as required.

8.4.6. 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.

Note: Pregnancy test must be performed even if the participant is menstruating at the time of the study visit.

All female participants will have a serum sample tested for β-human chorionic gonadotrophin (β-hCG) on admission to quarantine.

Blood samples will be tested for serum FSH in all post-menopausal female participants at screening.

8.4.7. 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.

Spirometry should meet the American Thoracic Society/European Respiratory Society guidelines criteria (Graham et al, 2019). For FEV_1 and forced vital capacity (FVC), the highest value from a minimum of 3 technically satisfactory attempts will be considered. For FEV_1 and FVC the highest and the second-highest value should not exceed more than 150 mL or 5% (whichever is greater). If the difference is larger, up to 8 technically acceptable measurements will be made with repeatability assessed after each additional attempt. If after 8 technically acceptable attempts the difference remains greater than 150 mL or 5% (whichever is greater) the highest values will be reported, and an operator comment will be made to the source data. Values for FEV_1 and FVC will be assessed and reported as the highest values regardless of curve.

Predicted values will be calculated according to the formula of the Report of the Global Lung Function Initiative, ERS Task Force Lung Function Reference Values (Quanjer et al, 2012).

Spirometry may be performed at any time in the event of respiratory signs or symptoms (repeated coughing, bradypnea, tachypnoea, rales, and rhonchi) or respiratory difficulties.

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 Event 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, it is judged by the PI/investigator to be no longer clinically significant, the participant is lost to follow-up (as defined in Section 7.3, Lost to Follow-up), or an alternative explanation has been provided. 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 regulatory and REC 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 to the regulatory authority, REC, and investigators.

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 describing an SAE or other specific safety information (e.g., summary or listing of SAEs) 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.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal distress, foetal death, stillbirth, congenital anomaly/birth defect, ectopic pregnancy) are considered SAEs.

8.6. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of RV299 as specified in the SoE. RV299 concentrations in nasal washes may be explored.

Further to emerging data on RV299, additional blood samples (within the blood volume limit) may be collected at additional time points during the study, if warranted and agreed upon between the PI/investigator and the sponsor. The timing of sampling may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

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 RV299. Samples collected for analyses of RV299 plasma concentration 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 plasma 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 RV299 will be collected according to the SoE, and processed and sent to the sponsor's PK vendor according to the AP.

8.6.2. Pharmacokinetic Parameters

Pharmacokinetic parameters of interest may include:

AUC_{τ}, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{½}$

Pharmacokinetic parameters will be calculated using non-compartmental methods. Parameters will be summarised descriptively.

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9. Statistical Considerations

9.1. Statistical Hypotheses

The primary statistical hypothesis is that treatment with RV299 will show an antiviral effect demonstrated by a significant reduction in RSV viral load AUC (measured by qRT-PCR) compared to placebo.

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9.3. Populations for Analyses

The following populations are defined in Table 9-1.

Table 9-1: Study Populations

Population	Description
Intent-to-treat (ITT) analysis population	All randomised participants who received challenge virus and at least 1 dose of IMP
Intent-to-treat infected (ITT-I) analysis population	All randomised participants who received challenge virus and at least 1 dose of IMP, and meet the criterion for laboratory-confirmed RSV infection
Intent-to-treat infected analysis population A (ITT-A)	All randomised participants who received challenge virus and at least 1 dose of IMP and meet the criterion for laboratory-confirmed RSV infection using only assessments prior to taking IMP
Intent-to-treat infected analysis population B (ITT-B)	All randomised participants who received challenge virus and at least 1 dose of IMP and meet the criterion for laboratory-confirmed RSV infection using only assessments after taking IMP
Per protocol (PP) analysis population	All ITT-I analysis population participants who have no major protocol deviations, and who completed the quarantine period up to the final day of quarantine (Day 12) and received all 10 doses of IMP

Population	Description
Safety analysis population	All randomised participants who received challenge virus and at least 1 dose of IMP
PK analysis population	All ITT analysis population participants with at least one post-dose PK result

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

The primary efficacy analysis population will be on the ITT-I analysis population, and the ITT-A, ITT-B, and PP analysis populations will be used for sensitivity analysis, as defined in the statistical analysis plan (SAP). The safety evaluation will be performed on the safety analysis population. 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.

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9.4.1. Statistical Analysis Plan

The SAP will be developed and finalised prior to database lock for the study. The finalised SAP will be signed prior to unblinding the study data. Full details of the planned statistical analysis will be presented in the SAP that will include a more technical and detailed description of the statistical analyses described in the current protocol section.

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 (CSR).

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9.4.2. General Considerations

9.4.2.1. Descriptive Statistics

Primary, secondary, CCI endpoints will be analysed descriptively.

Continuous variables will be summarised using number of available data, number of missing data, mean (and/or geometric mean, where applicable), SD, 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 5% 2-sided significance level, except if otherwise specified. No adjustment for multiple testing will be performed (see Section 9.1, Statistical Hypothesis).

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 Chi-square test (or 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 RV299, 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 blinded data review meeting, 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 will be computed for each study intervention arm as proportion of participants actually receiving IMP as prescribed. For each participant, the proportion of planned dose actually received will be computed.

9.4.4. Primary Efficacy Analysis

The primary efficacy analysis will be conducted on the ITT-I analysis population.

The main estimator of the primary endpoint, the median AUC of qRT-PCR viral load as determined on nasal samples (virology) starting at initial administration of investigational medicinal product (IMP) up to discharge from quarantine (Day 12), will be analysed on the ITT-I analysis population.

Descriptive statistics and the 95% CI will be presented by treatment arm. The differences between RV299 and the placebo arm will be analysed using the t-test or Wilcoxon rank sum test if the assumptions for the t-test are not met.

Further details will be provided in the SAP.

9.4.5. Secondary Efficacy Analysis

Secondary endpoints as outlined in Section 3, Objectives and Endpoints will be summarised by treatment arm. Inferential tests will be performed according to Table 9-2. Further details will be provided in the SAP.

Table 9-2: Analysis of Secondary Efficacy Endpoints

Endpoint	Analysis
Peak viral load by qRT-PCR	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). Inferential analysis: t-test or Wilcoxon rank sum test.
Time to confirmed negative test by qRT-PCR starting at initial administration of IMP	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). Kaplan Meier curves will be prepared. No inferential analysis.
Time to confirmed negative test by qRT-PCR starting from peak qRT-PCR after initial administration of IMP	
Time (days) to peak qRT-PCR in nasal samples, starting from initial administration of IMP	
VL-AUC of RSV challenge virus as determined by viral culture on nasal samples	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations).

Endpoint	Analysis
Peak viral load of RSV as defined by the maximum viral load determined by viral culture measurements in nasal samples starting from initial administration of IMP up to planned discharge from quarantine (Day 12, am).	Inferential analysis: t-test or Wilcoxon rank sum test.
Time (days) to confirmed negative test by viral culture measurements in nasal samples starting at initial administration of IMP	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). No inferential analysis.
Time (days) to confirmed negative test by quantifiable viral culture measurements in nasal samples starting from peak viral culture after initial administration of IMP	
Time (days) to peak viral culture in nasal samples, starting from initial administration of IMP	
TSS-AUC starting at initial administration of IMP	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). Inferential analysis: t-test or Wilcoxon rank sum test.
TSS-AUC-CFB starting at initial administration of IMP	
Peak TSS starting from initial administration of IMP	
Peak daily symptom score	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). No inferential analysis.
Time to symptom resolution starting at initial administration of IMP	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). No inferential analysis.
Time to symptom resolution starting at peak symptoms after initial administration of IMP	
Time to peak TSS	
Total weight of mucus produced	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). No inferential analysis
Total number of tissues used by participants	

AUC: area under the curve; qRT-PCR: quantitative reverse transcriptase-polymerase chain reaction; TSS: Total symptom score

CCI

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 most current version of the Medical Dictionary for Regulatory Activities and summarised descriptively by system organ class, preferred term, and study intervention arm for the number of AEs reported and the number and percentage of participants reporting each AE.

A by-participant AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided.

Other safety endpoints that will be presented by study intervention arm include laboratory evaluations (biochemistry, haematology, cardiac enzymes, and urinalysis), vital signs assessments, physical examinations, 12-lead ECG, and spirometry. Additionally, physical examinations will be listed.

9.4.8. Pharmacokinetic Analysis

Descriptive statistics will be calculated for the plasma concentrations of RV299 at each applicable time point and for the derived plasma PK parameters. Statistics include sample size (n), mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum.

For each participant, plasma concentration-time data of RV299 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

No interim analyses are planned for this study.

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 a 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 quarantine admission visit, 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 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. CCI [redacted]. 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.

CCI [redacted]

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 quality assurance 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 investigator and sponsor which includes ongoing safety oversight (to include 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 trial was registered.

The PI/investigator shall provide assurance to participants that their confidentiality will be maintained. CCI 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. Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (remote or on-site monitoring) are provided in the Monitoring Plan.

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.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the PI/investigator during the retention period as agreed with the sponsor and as required by local regulations or institutional policies.

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 entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The PI/investigator may need to request previous medical records or transfer of records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data for the study can be found in the Source Data Agreement.

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.

The PI/investigator is responsible for promptly informing the REC and providing the reason(s) for the suspension or termination of the study.

If the study is prematurely terminated, all study data must be returned to the sponsor. In addition, the site must conduct final disposition of all unused IMPs in accordance with the sponsor's procedures for the study.

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 Population.

Additional tests may be performed at any time during the study as determined necessary by the PI/investigator or required by local regulations.

Table 10-1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Haematology	Platelet count White blood cell count (absolute) White blood cell count differential: • Neutrophils • Lymphocyte • Monocytes • Eosinophils • Basophils Red blood cell count Reticulocyte count (% and absolute) Haemoglobin Haematocrit Mean corpuscular volume Mean corpuscular haemoglobin Mean corpuscular haemoglobin concentration
Coagulation	Prothrombin time Activated partial thromboplastin time
Biochemistry	Sodium Potassium Glucose Albumin Chloride Bicarbonate Calcium Uric acid Total protein Creatinine Total, direct, and indirect bilirubin Inorganic phosphate Blood urea nitrogen

Laboratory Assessments	Parameters
	C-reactive protein Gamma glutamyl transferase Alkaline phosphatase Alanine transaminase Lactate dehydrogenase Aspartate transaminase Urea
Thyroid function	Thyroid stimulating hormone at screening only Thyroxine at screening only
Cardiac enzymes	Creatine kinase Troponin (T)
Routine urinalysis	Colour Specific gravity Appearance pH Presence of blood, glucose, leukocytes, ketones, nitrites, proteins, urobilinogen, and bilirubin by dipstick If the dipstick yields potentially clinically significant abnormal results: microscopy, culture, and sensitivity examination
Other screening/eligibility tests	FSH* β-hCG* Urine pregnancy test* Urine drugs of abuse and cotinine Alcohol breath test Total cholesterol** Antibodies against HIV-1 and HIV-2 Hepatitis A immunoglobulin M** Hepatitis B surface antigen Hepatitis C antibodies Glycated haemoglobin** Immunoglobulin A antibodies**

* FSH only for post-menopausal female participants, β-hCG for all female participants, and urine pregnancy test only for female participants of childbearing potential.
**Optional at the discretion of the PI/investigator.

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded study staff until the study has been unblinded.

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

10.3.1. Adverse Event

AE Definition
An AE is defined as any untoward medical occurrence in clinical study participants administered a pharmaceutical (investigational or non-investigation) product. An AE does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product (definition as per ICH). This will also cover any AEs occurring after study intervention(s) including administration with the challenge agent in viral challenge studies.
Unsolicited AEs Unsolicited AEs are defined as any AEs observed by the participant or PI/investigator which are not pre-listed on the symptom diary card. Unsolicited AEs will be collected upon signature of study-specific ICF until the end of the study. Any unsolicited AEs observed by the PI/investigator and/or reported by the participant must be recorded in the eCRF regardless of causality in relationship with IMP.

Events Meeting the AE Definition
• Exacerbation of a pre-existing illness. • Increase in frequency or severity of a pre-existing episodic condition. • A condition detected or diagnosed after study intervention administration even though it may have been present prior to the start of the study. • A complication that occurs during a hospitalisation. • A clinically significant change in laboratory parameter.

Events NOT Meeting the AE Definition
• Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE. • Pre-existing disease or condition present or detected prior to start of study intervention administration that does not worsen (including screening findings such as abnormal laboratory results).

- Hospitalisation for elective surgery, social and/or convenience admissions provided they are arranged before the start of study intervention administration and the reason does not worsen.
- Over-administration of either the study intervention or concomitant medication without any signs or symptoms.
- An uncomplicated pregnancy or an induced elective abortion to terminate a pregnancy without medical reason.
- Typical/normal/solicited viral infection symptoms on symptom diary cards.
- Procedure-related events may be noted during the study while conducting nasal sampling (collection of nasal wash samples, nasopharyngeal swabs, or other nasal samples), specifically:
  - Nasal discomfort/irritation
  - Nasal abrasions
  - Nasal epistaxis
  - Sneezing
  - Watery eyes

  When mild in nature and as expected in the opinion of the PI/investigator or delegated physician, these events will not be reported as AEs.
- Asymptomatic bruising following venepuncture, or removal of an intravenous cannula.
- Dry lips and skin if solely due to the air-conditioning in the quarantine unit, with or without the use of emollients to maintain skin integrity.

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 The term 'life threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation • In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is an important medical event • Important medical events' – some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered as 'serious' in accordance with the above definition. • Medical judgement should be exercised in deciding whether an adverse event/reaction is serious. Important adverse events/reactions that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above occurring, should also be considered serious. Details of the SAE must be provided.

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.

Medical events will be assessed for expectedness against the reference safety information section of the Investigator's Brochure or equivalent, and any available Investigator's Brochure addendum. Any changes to the reference safety information will be deemed as a change to the risk/benefit profile and will require a substantial amendment to be submitted to the MHRA. This amendment must be approved before the changes are implemented in the study.

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

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. Adverse events will be fully recorded in the source documents as they are reported whether spontaneously reported by a participant or in response to questioning about wellbeing at each face-to-face study visit and during telephone calls. Enquiries about AEs should cover the period between the previous and current visit.

The following are examples of open-ended, non-leading questions that may be used to obtain this information:

- How are you feeling?
- Have you had any medical problems since your last visit/assessment?
- Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?

Following the reporting of AEs and concomitant medication, the PI/investigator should assess the participant's eligibility to continue in the study.

The PI/investigator will record all relevant information regarding an AE/SAE in the source documents and evaluate AEs/SAEs using the following guidelines:

- Description of event (if the event consists of a cluster of signs and symptoms, a diagnosis should be recorded)
- Seriousness
- Grade (or severity)
- Onset date and time
- Frequency

- Date and time of resolution (or 'continuing' if unresolved)
- Action taken
- Concomitant medication
- Clinical outcome
- Relationship or causality (IMP/challenge agent/study procedures/concomitant medication/other).

Any clinically significant abnormal laboratory result, vital sign or other measure will be followed until resolution (return to normal or baseline values), stabilisation, it is judged by the PI/investigator to be no longer clinically significant, the participant is lost to follow-up, or an alternative explanation has been provided.

If an AE is not resolved at the end of the study, the AE should be followed until it has resolved or (in the case of pregnancy) the pregnancy has been terminated (including spontaneous abortion), resulted in a birth, or a decision has been made by the sponsor that no further follow-up is required.

Even if the AE/SAE is assessed by the PI/investigator as not reasonably attributable to the challenge agent, its occurrence must be fully documented in the source notes.

10.3.6.2. Assessment

Description

If the event consists of a cluster of signs and symptoms, a diagnosis should be recorded (e.g., gastroenteritis) rather than each sign and symptom.

Onset and end

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

Assessment
Challenge Agent-related Symptoms The PI/investigator will assess, and review challenge agent-related symptoms recorded in participants' hVIVO symptom diary cards. Symptoms greater than Grade 0 will be expected and presumed to represent infection consequent to challenge agent inoculation and will not be additionally captured as AEs unless they meet the definition of an AE and are deemed to be clinically significant (in the opinion of the PI/investigator). Following challenge agent inoculation all unexpected (in the opinion of the PI/investigator) symptoms post inoculation will be captured as AEs, along with all other occurrences that meet the criteria for an AE.
Physical Examination Any clinically significant change in complete physical examination findings during the study will be documented as an AE.

Symptom-directed Physical Examination

Following challenge agent inoculation, URT symptoms (nasal discharge, otitis, pharyngitis, sinus tenderness) and LRT symptoms (abnormal breath sounds externally [e.g., stridor, wheezing] and on chest auscultation [rhonchi, crepitations or other]) will be expected and presumed to represent infection consequent to challenge agent and will not be additionally captured as AEs unless they meet the definition of an AE and are deemed to be clinically significant (in the opinion of the PI/investigator).

Vital Signs

Deterioration in a vital sign (compared to baseline) should only be reported as an AE if the deterioration fulfils the criteria for an AE. If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated vital sign will be considered as additional information.

Temperature

Following challenge agent inoculation, pyrexia (temperature ≥37.9°C) will be expected and presumed to represent infection consequent to challenge agent and will not be additionally captured as an AE unless it meets the definition of an AE and is deemed to be clinically significant (in the opinion of the PI/investigator) to be classed as an AE.

Following challenge agent inoculation all unexpected (in the opinion of the PI/investigator) pyrexia will be captured as an AE, along with all other occurrences that meet the criteria for an AE.

Spirometry

A 15% drop in a spirometry value (compared to baseline) confirmed by a repeat on the same day, will be a Grade 1 (mild) AE. The PI/investigator will use his/her clinical judgement to assign severity grades above Grade 1, based on evaluation of clinical signs and symptoms. If the repeated value has returned to normal an AE will not be raised.

Laboratory Values

Deterioration in a laboratory value (compared to baseline) should only be reported as an AE if the deterioration meets the criteria for an AE and is deemed to be clinically significant (in the opinion of the PI/investigator). If deterioration in a laboratory result is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result will be considered as additional information.

The PI/investigator and/or SME will judge whether abnormal laboratory values are clinically significant or not clinically significant, and record this in the source document. This entry should be signed and dated by the relevant PI/investigator. Laboratory abnormalities detected at screening will be considered as part of the medical history and will not be reported as AEs.

Challenge agent associated laboratory abnormalities (e.g., elevated alanine transferase, aspartate aminotransferase, or gamma glutamyl transferase; decreased neutrophils) may be recorded as AEs (at the discretion of the PI/investigator).

C-reactive Protein

Any value above 5 mg/L but less than 60 mg/L will be a Grade 1 (mild) AE (unless deemed non clinically significant by the PI/investigator). The PI/investigator will use his/her clinical judgement to assign severity grades above Grade 1, based on evaluation of clinical signs and symptoms.

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 CTCAE grading scale 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 CTCAE grading scale should be determined according to the definitions in Table 10-2.

Table 10-2: Classification of Adverse Events 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

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

The frequency of the AE should be categorised as one of the following:

- Single
- Intermittent
- Continuous

10.3.6.5. Assessment of Causality

- The PI/investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A 'reasonable possibility' of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The PI/investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The PI/investigator will also consult the Investigator's Brochure in his/her assessment.
- For each AE/SAE, the PI/investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the PI/investigator has minimal information to include in the initial report to the sponsor's pharmacovigilance (PV) provider. However, it is very important that the PI/investigator always assesses causality for every event before the initial transmission of the SAE data to sponsor's PV provider.
- The PI/investigator may change his/her opinion of causality considering follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The relationship of an AE to the IMP will be categorised as shown in Table 10-3:

Table 10-3: Classification of Adverse Events Relationship

Classification	Definition
Not related	The AE is related to an aetiology other than the IMP (the alternative aetiology must be documented in the participant's medical record).
Unlikely to be related	The AE is unlikely to be related to the IMP and likely to be related to factors other than IMP.
Possibly related	There is an association between the AE and the administration of the IMP, and there is a plausible mechanism for the AE to be related to the IMP, but there may also be alternative aetiology, such as characteristics of the participant's clinical status or underlying disease.
Probably related	A reasonable temporal sequence of the AE and the IMP administration exists and based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgement based on the PI/investigator's clinical experience, the association of the AE with the IMP seems likely.
Definitely related	A definite causal relationship exists between the AE and the administration of the IMP, and other conditions do not appear to explain the AE.

Unless an AE is 'definitely related' to the IMP, a causal relationship to one of the following should be considered, and full details provided on the AE reporting form as appropriate.

- Challenge agent

- Study procedures
- Concomitant medication
- Other

10.3.6.6. Action Taken

The PI/investigator should ensure that adequate medical care is provided to participants for any AEs/SAEs, including clinically significant laboratory values related to the study intervention. In addition, the PI/investigator will describe whether any treatment was given for the AE.

The PI/investigator will classify the action taken regarding the AE/SAE. The action taken should be classified according to the following categories and full details provided as appropriate:

- None
- Nondrug therapy given
- Concomitant medication taken
- IMP dose not changed
- IMP dose adjusted
- IMP administration temporarily interrupted
- IMP administration permanently discontinued
- Participant withdrawn
- Participant hospitalised
- Other.

10.3.6.7. Outcome

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

Table 10-4: Classification of Adverse Events Outcome

Classification	Definition
Resolved	Resolution of the AE with no residual signs or symptoms
Resolved with sequelae	Resolution of the AE with residual signs or symptoms
Ongoing	Either incomplete improvement or no improvement of the AE, such that it remains ongoing
Fatal	Outcome of the AE was death. 'Fatal' should be used when death was at least possibly related to the AE
Unknown (e.g., lost to follow-up)	Outcome of the AE is not known (e.g., the participant is lost to follow-up)

10.3.6.8. Follow-up

All AEs/SAEs must be followed up by the PI/investigator for follow-up until they are:

- Resolved (return to normal or baseline values), or
- Stabilised, or
- Judged by the PI/investigator to be no longer clinically significant, or
- The participant is lost to follow-up, or
- An alternative explanation has been provided.

Where appropriate, the participant may be referred to the participant's GP or other healthcare professional.

Additional measurements and/or evaluations may be necessary to investigate the nature and/or causality of an AE/SAE. This may include additional laboratory tests, diagnostic procedures, histopathological examinations, or consultation with other healthcare professionals. If the participant dies, any post-mortem findings (including histopathology) will be provided to the sponsor if possible.

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 regulatory and REC reporting obligations for the study. If the PI/investigator does not have all of the details regarding the SAE, he/she will not wait until this information becomes available before making the initial report to sponsor. Contact details are detailed in Table 10-5.

Notification should be made:

- By email to Syneos Health as soon as possible and within 24 hours of the PI/investigator being made aware of the event.
- In a detailed written report within 24 hours of the PI/investigator becoming aware of the event, using the Syneos Health Serious Adverse Event Report.

All reports should be directed to sponsor's PV provider, Syneos Health. The PI/investigator at the site is responsible for ensuring that a member of the sponsor study team is made aware of any SAE reports that have been transmitted.

Table 10-5: Contact Details for Reporting All Serious Adverse Events

Contact	Details
Name of sponsor's medical expert:	PPD
SME SAE telephone number:	PPD
Pharmacovigilance reporting email:	PPD
SAE email address:	PPD

In addition, any AE resulting in permanent study discontinuation for a participant, even if not serious and regardless of expectedness or causality, must be reported by telephone, email, or fax to the sponsor within 7 calendar days of the PI/investigator or any other investigator site staff's knowledge of the event.

The SAE form, AE record, and relevant concomitant medication record should be emailed to the sponsor's PV provider, Syneos Health, within 24 hours of the PI/investigator or any investigator site staff's knowledge of an SAE. An updated SAE report form should be forwarded to the sponsor within 24 hours of receipt of the new/updated information as relevant.

Information relating to the participant's subsequent medical progress must be submitted to the sponsor's PV provider, Syneos Health, as available, until the SAE has subsided or, in the case of permanent impairment, until it stabilises, and the overall clinical outcome has been ascertained.

The PI/investigator will also provide additional information, including a copy of the following documents (where applicable):

- Copies of test results, as available
- Hospital discharge summary (as soon as it is available to the PI)
- Autopsy report (as soon as it is available to the PI).

The PI/investigator must report SAEs/SUSARs to the relevant REC in accordance with applicable regulatory requirements and within the relevant timelines.

The REC will be sent annual safety updates in order to facilitate their continuing review of the study.

10.3.8. Reporting of Suspected Unexpected Serious Adverse Reaction

The sponsor is responsible for assessing SUSARs, unblinding potential SUSARs, and reporting SUSARs to the MHRA and REC.

The sponsor shall ensure that all relevant information about a SUSAR that occurs during a clinical study in the UK and is fatal or life threatening, is reported as soon as possible to the MHRA and the REC. This needs to be done within 7 calendar days after the sponsor became aware of the event. Any additional relevant information should be sent within 8 days of the first report being sent.

The sponsor shall ensure that a SUSAR which is not fatal, or life threatening is reported as soon as possible and in any event within 15 calendar days after the sponsor became aware of the event.

The procedure of SAE/SUSAR reporting will be described in a Safety Management Plan that will be finalised before the start of the study to define the different tasks of the investigator, CCI (the sponsor) and Syneos Health (acting on behalf of CCI).

10.3.9. Adverse Reactions to Non-investigational Medicinal Products

Any AEs/SAEs which are related to/caused by a concomitant medication or challenge agent, should not be classed as adverse reactions, serious adverse reactions, or SUSARs (adverse reactions, serious adverse reactions, SUSARs relate only to IMP by definition). However, an SAE caused by a non-IMP would need to be reported to the MHRA/REC and participants must be followed up until the event is considered resolved, judged by the PI/investigator to be no longer clinically significant, the participant is lost to follow-up, an alternative reason has been provided, or until the PI in conjunction with the sponsor deem the event stable and a decision for no further follow-up has been taken (see Section 10.3.6.7, Outcome, and Section 10.3.6.8, Follow-up).

10.3.10. Post-study Adverse Events and Serious Adverse Events

All SAEs that occur during the study from ICF signature until last participant last scheduled visit must be reported by the PI/investigator to Syneos Health as soon as possible, in accordance with hVIVO SOPs, and at the latest within 24 hours of becoming aware of the event.

All AEs/SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed up until the event is considered resolved, judged by the PI/investigator to be no longer clinically significant, the participant is lost to follow-up, an alternative reason has been provided, or until the PI in conjunction with the sponsor deem the event stable and a decision for no further follow-up has been taken (see Section 10.3.6.8, Follow-up).

10.3.11. Pregnancy

If a female participant or female partner of a male participant becomes pregnant during of the study, this must be reported by the PI/investigator to the SME and study monitor by telephone as soon as possible, in accordance with hVIVO SOPs, and at the latest within 24 hours of becoming aware of the event.

Following the telephone notification, the PI/investigator must fully and accurately complete the appropriate pregnancy reporting form, which must be emailed to the SME and the study monitor at the latest within 24 hours of becoming aware of the pregnancy.

Participants will be advised to contact their GP or a specialist, as appropriate.

Consent for follow-up of the pregnancy and pregnancy outcome will be sought from the pregnant study participant or the pregnant partner of the male study participant as applicable. Consent for follow-up will be documented on an hVIVO Pregnancy Follow-up ICF.

Provided that the appropriate consent is in place, information related to the pregnancy will be collected as per hVIVO SOPs and the sponsor's requirements. The completed reporting form(s) will be sent to the sponsor for review and assessment, and subsequent reporting as required.

- A complete evaluation will be documented in the source data to permit transfer to the clinical database.
- The emergency code break envelopes will be requested (Section 6.3, Randomisation and Blinding) to break the blind for the appropriate study participant to ensure that further care can be based on the actual identity of the study intervention that the participant received.
- hVIVO will maintain contact with the participant for a protracted period, but certainly until after the birth, in order to assess for outcomes that may be reportable as related AEs, and for reporting to the sponsor as appropriate.
- hVIVO, in consultation with the participant, will keep the participant's GP informed.
- All cases of foetal drug exposure via the parent as a study participant will be reported to the sponsor and the REC.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal distress, foetal death, stillbirth, congenital anomaly/birth defect, ectopic pregnancy) are considered SAEs.

10.4. Appendix 4: Normal Ranges

Vital signs normal ranges

Vital Signs	Lower Limit	Higher Limit	Units
Tympanic temperature (above 37.8 classed as pyrexia)	35.5	37.8	°C
Oxygen saturation	Normal is ≥95		%
Respiratory rate	10	20	breaths per minute
Heart rate	40	100	beats per minute
Systolic BP	90	140	mmHg
Diastolic BP	50	90	mmHg

ECG

ECG Parameters	Lower Limit	Higher Limit	Units
HR	40	100	bpm
QRS	60	120	ms
PR interval	120	220	ms
QT	320	450	ms
QTc (Fridericia/Bazett)	320	<450 (females)	ms
		<430 (males)	

Spirometry

Spirometry Parameters	Lower Limit	Higher Limit	Units
FEV_1	Normal if ≥80% of the predicted value		litres
FEV_1/FVC	Normal if ≥70% (≥0.7) of the predicted value		litres

No single value should be used in isolation, all spirometry reference ranges require physician interpretation of the participant's overall status to determine their relevance.

CCI [redacted]

[redacted]

10.6. Appendix 6: Abbreviations

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AP	Analytical plan
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{0-24h}	Area under the plasma concentration-time curve over the last 24 hours dosing interval
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{τ}	Area under the plasma concentration-time curve from time zero to the end of the dosing interval
BCRP	Breast cancer resistance protein
BID	bis in die, twice a day
β-hCG	β-human chorionic gonadotrophin
BMI	Body mass index
BP	Blood pressure
cGMP	current Good Manufacturing Practice
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
$FEV_{(1)}$	Forced expiratory volume (in 1 second)
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General practitioner
HIV	Human immunodeficiency virus
HR	Heart rate
HVC	Human viral challenge
IC_{50}	50% inhibitory concentration
ICF	Inform consent form
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
ITT	Intent-to-treat
ITT-I	Intent-to-treat infected
ITT-A	Intent-to-treat infected analysis population A
ITT-B	Intent-to-treat infected analysis population B
LRT	Lower respiratory tract
LRTI	Lower respiratory tract infections
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	messenger RNA

Abbreviation	Term
NOAEL	No-observed-adverse-effect-level
PCR	Polymerase chain reaction
PFU	Plaque-forming unit
P-gp	P-glycoprotein
PHQ	Patient Health Questionnaire
PI	Principal investigator
PK	Pharmacokinetic(s)
PP	Per protocol
CCI	[redacted]
[redacted]	[redacted] on
REC	Research Ethics Committee
RNA	Ribonucleic acid
RR	Respiratory rate
RSV	Respiratory syncytial virus
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SD	Standard deviation
CCI	[redacted]
SEM	Standard error of the mean
SME	Sponsor's medical expert
SoE	Schedule of events
SOP	Standard operating procedure
SUSAR	Suspected unexpected adverse reaction
$t_{1/2}$	Terminal half-life
t_{max}	Time to maximum plasma concentration
TSS	Total symptoms score
TSS-AUC	Area under the curve over time of total clinical symptoms
TSS-AUC-CFB	Area under the curve over time of total clinical symptoms change from baseline
UK	United Kingdom
URT	Upper respiratory tract
USA	United States of America
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 inoculation 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 inoculated. 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, unless otherwise specified by the protocol.
First study visit (of a participant)	The visit in which the study-specific consent is signed.
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
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 [redacted]
Viral shedding (for dosing)	1 positive detection by qicPCR

TERM	CRITERIA
CCI [redacted]	[redacted] • [redacted] • [redacted] [redacted]

10.8. Appendix 8: Protocol Amendment History

Protocol Amendment Summary of Changes Table

PROTOCOL HISTORY		
Document	**Date**	**Amendment Type**
Initial Clinical Trial Protocol (v1.0)	06May2022	Not applicable. First Version.
Amendment 01 (v2.0)	28Jul2022	Substantial Amendment
Amendment 02 (v3.0)	31Oct2022	Substantial Amendment

Amendment 02 (31-Oct-2022)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Principal Investigator Signatory (p.3) & Study Staff Contact Information(p.4)	Principal Investigator (PI) name and contact details updated to reflect the change in PI from P [redacted] P	Substantial Amendment to the Protocol to document change in PI.

Amendment 01 (28-Jul-2022)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Principal Investigator Signatory (p.3) & Study Staff Contact Information(p.4)	Principal Investigator (PI) name and contact details updated to reflect the change in PI from P [redacted] P	Substantial Amendment to the Protocol to document change in PI.
Section 1.2 Schedule of Events (SoE) (p.23)	Removal of Directed Physical Exam (DPE) from the Schedule of assessments for the Early Withdrawal visit as a Complete Physical Exam will be performed and therefore DPE is not required.	

Section 1.2 Key notes for time and events schedule (p.26)	Clarification added to key note ‘e’ to confirm the 60-hour, 72-hour, 84-hour, and 96-hour timepoint PK samples may be omitted, as applicable, if it occurs after discharge, for participants who commence dosing on Day 4 and Day 5.	Minor administrative changes for clarification.

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