[redacted]

Clinical study protocol

A RANDOMIZED, PHASE 2A, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS AND ANTIVIRAL ACTIVITY OF MULTIPLE DOSES OF ORALLY ADMINISTERED EDP-323 AGAINST RESPIRATORY SYNCYTIAL VIRUS INFECTION IN THE VIRUS CHALLENGE MODEL IN HEALTHY ADULTS

Brief Title:	A controlled Phase 2a study to evaluate the efficacy of EDP-323 against respiratory syncytial virus infection in a virus challenge model
Protocol Version and Date:	Final version 2.0; 25-Mar-2024
Sponsor:	ENANTA Pharmaceuticals, Inc. 500 Arsenal Street Watertown, MA 02472 United States of America
Protocol Number:	EDP 323-101
hVIVO Study Number	ETP-CST-001
Compound:	EDP-323 capsules for oral administration
IRAS ID:	1007761

Confidentiality and Protections Statement:

This document contains confidential information of hVIVO and ENANTA Pharmaceuticals, Inc. This document must not be disclosed to anyone other than the study staff and members of the Independent Ethics Committee/Institutional Review Board or Competent Authorities. The information in this document cannot be used for any purpose other than the conduct or evaluation of the clinical investigation without the prior written consent of hVIVO and ENANTA Pharmaceuticals, Inc.

Personal data included in the protocol is subject to the United Kingdom (UK) Data Protection Act considerations and protections.

[redacted]

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

Name, title (typed or printed): [redacted]

Signature and Date: 3/27/2024	[redacted]

Investigator Agreement

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

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

Principal Investigator Signatory

Name (typed or printed): [redacted]

Signature and Date: 3/27/2024	[redacted]

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

[redacted]

Study Staff Contact Information

Contact	Details
Sponsor	ENANTA Pharmaceuticals, Inc. 500 Arsenal Street Watertown, MA 02472 United States of America
Sponsor's representative	[redacted]
Principal Investigator and Clinical Study Facilities	[redacted] hVIVO Services Limited Queen Mary BioEnterprises Innovation Centre 42 New Road, London E1 2AX, United Kingdom (UK) hVIVO Services Limited The Whitechapel Clinic 49-53 New Road, London E1 1HH, UK hVIVO Services Limited 21 Plumbers Row, London E1 1EQ, UK hVIVO Services Limited 36 George Street, Manchester M1 4HA, UK [redacted]
Sponsor's Medical Expert/Medical Monitor	[redacted]
Key Protocol Contributors	Refer to the local study contact list document

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1. SYNOPSIS

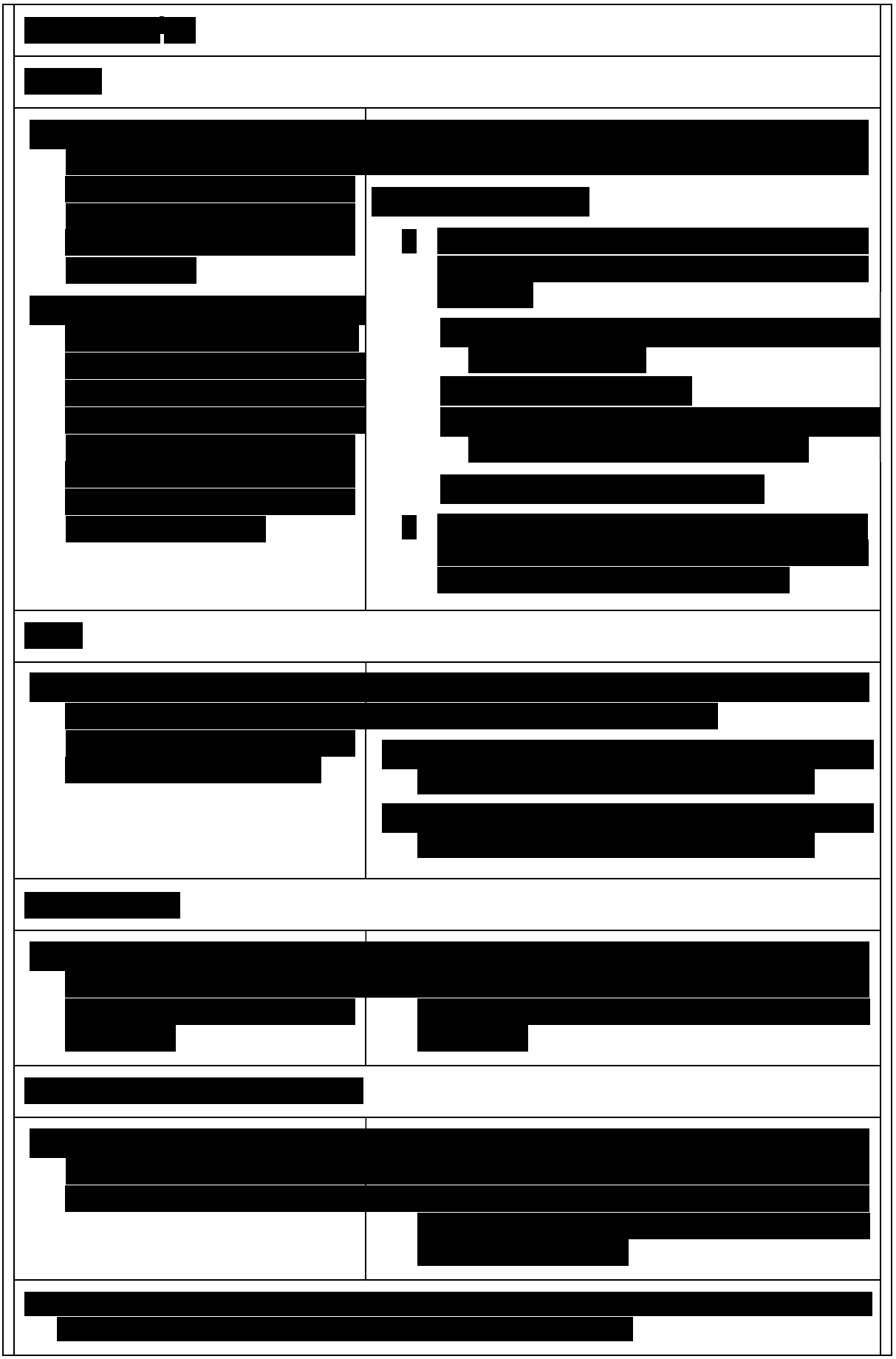
Study Title:	**A Randomized, Phase 2a, Double-blind, Placebo-controlled Study to Evaluate the Safety, Pharmacokinetics and Antiviral Activity of Multiple Doses of Orally Administered EDP-323 Against Respiratory Syncytial Virus Infection in a Virus Challenge Model in Healthy Adults**
Short Title	A controlled Phase 2a study to evaluate the efficacy of EDP-323 against respiratory syncytial virus infection in a virus challenge model
Protocol Number:	EDP 323-101
hVIVO Study Number:	ETP-CST-001
Sponsor	ENANTA Pharmaceuticals, Inc
IRAS ID	1007761
Study Phase:	Phase 2a
Clinical Study Facilities	hVIVO Services Limited Queen Mary BioEnterprises Innovation Centre 42 New Road, London E1 2AX, United Kingdom (UK) hVIVO Services Limited The Whitechapel Clinic 49-53 New Road, London E1 1HH, UK hVIVO Services Limited 21 Plumbers Row, London E1 1EQ, UK hVIVO Services Limited 36 George Street, Manchester M1 4HA, UK
Study Type	Interventional
Indication	Respiratory syncytial virus (RSV) infection
Design	This is a randomized, Phase 2a, double-blind, placebo-controlled study to evaluate the safety, pharmacokinetics (PK), and antiviral activity of multiple doses of orally administered EDP-323 against RSV infection in healthy adults after challenge with RSV-A Memphis 37b. The study will test 2 doses of EDP-323: EDP-323 high dose (600 mg once daily [QD] for 5 days) vs EDP-323 low dose (600 mg loading dose for 1 day followed by 200 mg QD for 4 days).

Objectives and Endpoints

Objectives	**Endpoints**
Primary:	
Efficacy	
• To evaluate the antiviral activity of EDP-323 compared to placebo in healthy adult participants inoculated with RSV-A Memphis 37b	• Reduction in RSV area under the viral load-time curve (VL-AUC) measured by quantitative reverse transcription-polymerase chain reaction (qRT-PCR) in nasal samples
Secondary:	
Efficacy	
• To further evaluate the antiviral activity of EDP-323 compared to placebo in healthy adult participants inoculated with RSV-A Memphis 37b • To evaluate the clinical disease severity in healthy adult participants inoculated with RSV-A Memphis 37b followed by administration of EDP-323 compared to placebo	• Viral load: ○ RSV viral load by qRT-PCR of nasal samples, including: • Reduction in RSV peak viral load (VLPEAK) • Reduction in time to RSV VLPEAK after first dosing • Time to RSV viral load negativity after first dosing • Time to first negative slope of RSV viral load after first dosing • Slope of the RSV viral load over time (clearance rate) from time of RSV VLPEAK to 1, 2, 3, and 4 days later ○ RSV viral load by cell culture (plaque assay) of nasal samples, including: • Reduction in RSV VL-AUC • Reduction in RSV VLPEAK • Reduction in time to RSV VLPEAK after first dosing • Time to RSV viral load negativity after first dosing • Time to first negative slope of RSV viral load after first dosing • Slope of the RSV viral load over time (clearance rate) from time of RSV VLPEAK to 1, 2, 3, and 4 days later

	• Clinical symptoms and disease severity:
	  ○ Effect on RSV symptoms using the symptom diary card [SDC]), with endpoints including:
	  • Reduction in area under the total symptom score (TSS)-time curve (TSS-AUC)
	  • Reduction in peak TSS
	  • Time to return to baseline (last assessment before RSV inoculation) TSS
	  • Reduction in time to peak TSS
	  ○ Total weight of nasal discharge (mucus) produced
	  ○ Total number of tissues used

Pharmacokinetics	
• To evaluate the PK profile of EDP-323 (and metabolites) in blood samples in healthy adult participants inoculated with RSV-A Memphis 37b • To characterize the relationship between plasma PK of EDP-323 and VL-AUC (qRT-PCR) and TSS-AUC in healthy adult participants inoculated with RSV-A Memphis 37b	• EDP-323 (and metabolites) concentrations and PK parameters in blood samples: maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), apparent systemic clearance (CL/F), terminal elimination rate constant (λ_z), volume of distribution (Vd/F), plasma concentration at 12 hours (C_{12h}), plasma concentration at 24 hours (C_{24h}), area under the concentration-time curve from time 0 to time of last quantifiable concentration (AUC_{last}), area under the concentration-time curve over the dosing interval ($AUC_{0\text{-}tau}$), and area under the concentration-time curve from time 0 to infinity ($AUC_{0\text{-}\infty}$), and other parameters as applicable • EDP-323 plasma PK (area under the curve [AUC]) correlations with VL-AUC (e.g., qRT-PCR) and TSS-AUC
Safety	
• To evaluate the safety of EDP-323 in healthy adult participants inoculated with RSV-A Memphis 37b	• Occurrence of adverse events (AEs) from initial administration of investigational medicinal product (IMP) up to discharge • Occurrence of AEs from initial administration of IMP up to Day 28 follow-up • Occurrence of serious adverse events (SAEs) from initial administration of IMP up to Day 28 follow-up



Hypothesis	The primary statistical hypothesis is that treatment with EDP-323 will show an antiviral effect demonstrated by a significant reduction in RSV VL-AUC (measured by qRT-PRC in nasal samples) compared to placebo.
Investigational Medicinal Product (IMP)	EDP-323 capsules and placebo capsules for oral administration, to be administered once daily (QD) for a total dosing period of 5 days • High dose: 600 mg EDP-323 QD for 5 days • Low dose: 600 mg EDP-323 (loading dose) for 1 day, followed by 200 mg EDP-323 QD for 4 days
Challenge Agent	RSV-A Memphis 37b
Challenge Agent Route	Intranasal delivery
Challenge Agent Titer	Total dose of approximately 4 $\log_{10}$ plaque-forming units (PFU)
Study Population	Healthy male and female participants aged between 18 to 55 years, who are pre-screened during the hVIVO generic screening process to document low antibody levels to RSV and to therefore be susceptible to RSV infection ("serosuitable") and who meet the study-specific inclusion / exclusion criteria.
Summary of Study Design	This is a randomized, Phase 2a, double-blind, placebo-controlled study to evaluate the safety, PK, and antiviral activity of multiple doses of orally administered EDP-323 against RSV infection in healthy adults after challenge with RSV-A Memphis 37b. In this study, 2 doses of EDP-323 will be tested: EDP-323 high dose (600 mg QD for 5 days) vs low dose (600 mg loading dose for 1 day followed by 200 mg QD for 4 days). The study will have a placebo arm. Due to its exploratory nature, no adjustment will be made to the type 1 error in this proof-of-concept study. The study is divided into the following study phases: **Screening**: • Screening prior to inoculation with challenge virus from Day -90 to Day -2/-1. **Inpatient Phase:** • Participants will be resident in the quarantine unit for approximately 15 days, from admission on Day -2/-1 to planned discharge on Day 12. Discharge from quarantine is foreseen at Day 12 if the participant has no clinically significant symptoms. The detection of virus by RSV

	discharge test (e.g., qualitative rapid viral antigen test [RVAT]) will be performed at investigator's discretion. If the participant continues to have clinically significant symptoms, additional extended quarantine stay may be required based on the assessment of the PI/investigator. Procedures will include: • **Pre-human Viral Challenge**: o Admission to quarantine unit on Day -2/-1. o Baseline assessments will be conducted as per Schedule of Events (SoE) up to Day 0, pre-challenge. • **Human Viral Challenge**: o RSV-A Memphis 37b virus inoculation on Day 0. • **Post-human Viral Challenge**: o Randomization to receive EDP-323 (high dose or low dose) or matched placebo. o Administration of IMP (EDP-323 or placebo). IMP administration will be initiated (triggered) by a positive RSV result (measured by qualitative integrative cycler [qic] PCR) between Day 2 and Day 5 AM (nasal sampling twice daily, morning and evening; on Day 5 only in the morning). Dosing will start approximately 12 hours after first detection of RSV. If no positive RSV result is obtained, dosing will start in the evening of Day 5. Duration of treatment with EDP-323 (or placebo) will be 5 days (QD) in the period from Days 2 to 9, with the start day dependent on RSV result. o Day 1 onwards and each day – study assessments will be conducted as per SoE. o Discharge from quarantine is planned on Day 12 post inoculation. **Outpatient Phase:** • Follow-up visit: Day 28 (±3 days) Details of the activities to occur during the study are provided in the SoE.
Randomization	In this study, 132 participants will be randomized 1:1:1 into one of 3 treatment groups (n=44 each) to receive EDP-323 (at 2 different doses) or placebo.
Participant Replacement Policy	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 PI/investigator and sponsor. The replacement participant will receive the same intervention as the participant being replaced. The replacement participant will be assigned a new, unique randomization number. The replacement participant will receive the same allocated, blinded treatment as the participant who is being replaced.
Expected Duration of Participation per Participant	Up to 4 months, from screening to the participant's last scheduled follow-up visit.
Overall Duration of Clinical Phase	The length of the clinical phase is expected to be approximately 8 months from first participant's planned first study visit (admission to the quarantine unit on Day -2/-1) to the last participant's last scheduled study visit (last scheduled follow-up visit on Day 28 [±3 days]).
End-of-Study Definition	The end of the study is defined as the date of the last visit of the last participant in the study.
Sample Size Determination	The statistical powering selected for this study is estimated to be sufficient for the primary objective and the primary endpoint and important secondary endpoints. The sample size was calculated based on the assumptions of a 55% reduction in qRT-PCR VL-AUC, with a 72% coefficient of variation (CV) (based on similar previous studies), for a power of 80% and a 2-sided 5% level of significance (without adjustment for multiple comparisons) and assuming a 70% infectivity rate (based on similar previous studies). On this basis, it is estimated that 31 evaluable RSV infected (intent-to-treat infected [ITT-I]) participants per arm and 44 inoculated participants would be sufficient for the study to demonstrate an antiviral affect as measured by qRT-PCR with a power of at least 80% (achieved power computed as 84.1%). However, with the more conservative assumption of a 63% infection rate, 44 recruited participants, resulting in 28 infected participants would allow to detect a 55% relative reduction in qRT-PCR VL-AUC with at least 80% (80.2%) power. The sample size of 44 participants per arm would allow to detect a decrease of 75% in TSS-AUC (CV of 92.9%) and 55% in TSS peak score (CV of 68.8%) with more than 80% power (87.8% and 87.2% respectively) assuming an infection rate of 70% (31 infected participants). The more conservative assumption of a 63% infection rate (28 infected participants) would allow to detect a 75% relative reduction in TSS-AUC and 55% in peak-AUC with respectively 84.3% and 83.6% power.
Statistics	Primary efficacy analysis: the main estimator of the primary endpoint, the mean or median VL-AUC of RSV-A Memphis 37b, depending on whether the endpoint is normally distributed, as

determined by qRT-PCR on nasal samples (virology) collected twice daily starting 2 days post-viral challenge (Day 2) up to discharge from quarantine, will be analyzed on the ITT-I analysis set.

The calculation of the VL-AUC will be performed on log_{10}-transformed PCR data using the trapezoidal summation rule based on actual time intervals in hours. Results below the lower limit of quantification (LLOQ) will be given values as detailed in the statistical analysis plan (SAP).

Descriptive statistics and the 95% confidence intervals (CI) will be presented by treatment group. The differences between each active treatment group and the placebo arm will be analyzed using the t-test or Wilcoxon rank sum test, depending on whether the endpoint is normally distributed.

Full details of the planned analysis will be presented in the SAP. Any deviations from the SAP will be documented in the clinical study report.

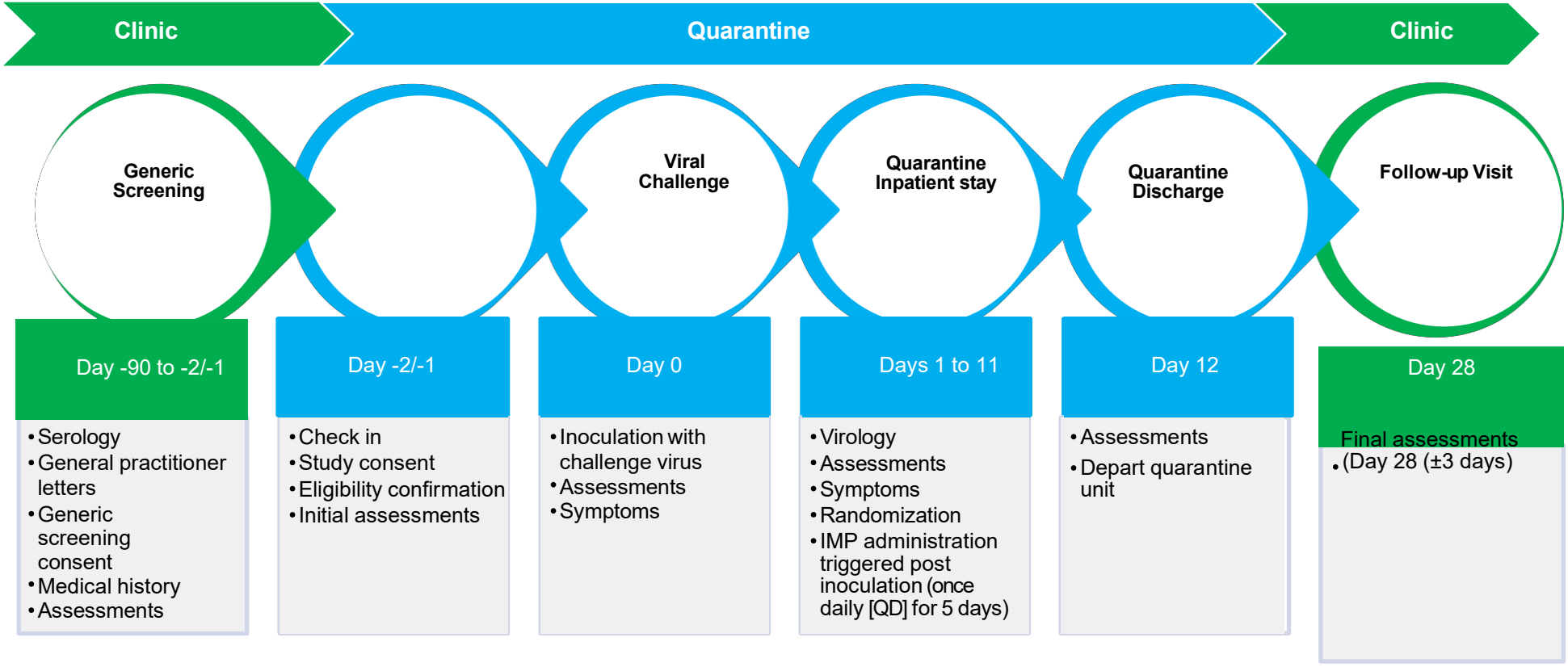
Study Analysis Sets:

Participant Analysis Set	**Description**
Enrolled	A participant will be considered as 'enrolled' into the study once he/she has been inoculated with the challenge virus.
Intent-to-treat (ITT) analysis set	All participants having received challenge virus, randomized, and having received at least one dose of IMP.
Intent-to-treat infected (ITT-I) analysis set	All participants having received challenge virus, randomized, and having received at least one dose of IMP, and meeting the criterion for laboratory-confirmed RSV infection (see below for definition of laboratory-confirmed RSV infection). The ITT-I analysis set will be considered the primary analysis population for efficacy endpoints. A participant will fulfil the criteria for laboratory-confirmed RSV infection if: • At least 2 positive detections by viral load qRT-PCR assay specific for the challenge virus, reported within 2 consecutive study days. and/or

		• One positive detection by viral load qRT-PCR assay, specific for the challenge virus, in which an aliquot of the same sample has also tested positive in a cell-based infectivity assay appropriate for detecting the challenge virus.
	Intent-to-treat infected pre-dose (ITT-A) analysis set	All participants having received challenge virus, randomized, and having received at least one dose of IMP, and meeting the criterion for laboratory-confirmed RSV infection (as per ITT-I) while using only assessments prior to taking IMP. The ITT-A analysis set will be considered a secondary analysis population for efficacy endpoints. ITT-A will be a subset of ITT-I.
	Intent-to-treat infected post-dose (ITT-B) analysis set	All participants having received challenge virus, randomized, and having received at least one dose of IMP, and meeting the criterion for laboratory-confirmed RSV infection (as per ITT-I) while using only assessments after taking IMP. The ITT-B analysis set will be considered a secondary analysis population for efficacy endpoints. ITT-B will be a subset of ITT-I.
	Per protocol (PP) analysis set	All ITT-I analysis set participants who have no major protocol deviations, and who complete the quarantine period up to the final day of quarantine and receive all doses of IMP. Participant exclusions will be determined at a blinded data review meeting (BDRM), which will take place prior to database lock. The PP analysis set will be considered a secondary analysis population for efficacy endpoints.
	Safety analysis set	All participants having received challenge virus, regardless of whether they received IMP or not.
	Pharmacokinetics (PK) analysis set	All ITT analysis set participants with at least one post-dose PK result. The PK analyses will be performed on the PK analysis set.

	The study being exploratory by nature, aiming at assessing the true biological effect of the IMP used in the best experimental conditions and not the effectiveness of the strategy to treat participants with the IMP in conditions closest to real life, the primary efficacy analysis will be on the ITT-I analysis set. The ITT-A, ITT-B, and PP analysis sets will be considered a secondary analysis population for efficacy endpoints, as defined in the SAP. The safety evaluation will be performed on the safety analysis set. Additional analysis sets may be defined in the SAP.

1.1. Study Schematic: On-study Participant Progression



NOTES:

- Screening assessments (including repeats, as required) may be performed up to Day -1 at the discretion of the Pl/investigator and in accordance with the design of the study.
- Discharge from quarantine is foreseen at Day 12 if the participant has no clinically significant symptoms. The detection of virus by respiratory syncytial virus (RSV) discharge test (e.g., qualitative rapid viral antigen test [RVAT]) will be performed at PI/investigator's discretion. If the participant continues to have clinically significant symptoms, additional extended quarantine stay may be required based on the assessment of the PI/investigator. If the participant decides to leave against medical advice, the participant will be discharged as per hVIVO standard operating procedures (SOPs), with consideration to include appropriate personal protective equipment, transport, and instructions on contact with vulnerable individuals. The participant will be advised to refer himself/herself to their general practitioner (GP) if they need treatment following discharge. If clinically indicated, the PI or delegated study physician will schedule follow-up calls with the participant every 1 or 2 days until symptoms resolved.

1.2. Schedule of Events (SoE)

Study Phase	Screening*	Inpatient Phase Quarantine																Outpatient Phase Follow-up	Early Withdrawal (p)
Study Day (with respect to challenge virus inoculation)	Day -90 to Day –2/-1	Admission Day -2/-1 (o)	Day -1°	Day 0 Pre-Challenge	Day 0 Challenge	Day 0 Post-Challenge	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 28 (±3 days) (Final Follow-up	Post-Challenge
Written consent (a)	X	X																		
Eligibility criteria (b)	X	X		X																
Medical & medication history	X	X																		
Demographics	X																			
Height & weight, body mass index (BMI) (c)	X	X																(X)	(X)	(X)
Patient Health Questionnaire (PHQ-9)	(X)	(X)																		
Generalized Anxiety Disorder Questionnaire (GAD-7)	(X)	(X)																		
Alcohol breath test	X	X																	X	
Urinalysis	X	X																X	X	X
Urine drugs of misuse and cotinine screen	X	X																	X	
Urine pregnancy test (female participants of childbearing potential)	X																	X	X	X
Spirometry	X																			
12-lead electrocardiogram (ECG)	X	X											X				X		X	X
Complete physical examination	X	X																X	X	X
Symptom-directed physical examination (including nasal)			(X)	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)			

Study Phase	Screening[a]	Inpatient Phase Quarantine																Outpatient Phase Follow-up	Early Withdrawal (p)
Study Day (with respect to challenge virus inoculation)	Day -90 to Day –2/-1	Admission Day -2/-1 (o)	Day -1[o]	Day 0 Pre-Challenge	Day 0 Challenge	Day 0 Post-Challenge	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 28 (±3 days) (Final Follow-up	Post-Challenge
Vital signs (heart rate [HR], respiratory rate [RR], systolic and diastolic blood pressure [BP], peripheral arterial oxygen saturation [SpO_2]), temperature	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
hVIVO Symptom diary card (SDC) (e)		X	3X	3X			3X	3X	3X	3X	3X	3X	3X	3X	3X	3X	3X	X		
Respiratory Infection Intensity and Impact Questionnaire [RiiQ]) (e)		X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		
24-hour tissue count & nasal discharge weight (f)			X	X			X	X	X	X	X	X	X	X	X	X	X	X		(X)
Product Administration																				
Randomization (g)								(X)	(X)	(X)	(X)									
Investigational medicinal product (IMP) (EDP-323 or placebo) dosing (m)								(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)					
Challenge virus inoculation					X															
Collection of Blood Samples																				
Serum follicle-stimulating hormone (FSH) (postmenopausal women)	X																			
Serum beta-human chorionic gonadotrophin (β-HCG) pregnancy test (all female participants)		X																		
Human immunodeficiency (HIV), hepatitis B & C serology	X																			
Hematology (i)	X	X								X			X				X	(X)	X	X

Study Phase	Screening[f]	Inpatient Phase Quarantine																	Outpatient Phase Follow-up	Early Withdrawal (p)
Study Day (with respect to challenge virus inoculation)	Day -90 to Day –2/-1	Admission Day -2/-1 (o)	Day -1[o]	Day 0 Pre-Challenge	Day 0 Challenge	Day 0 Post-Challenge	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 28 (±3 days) (Final Follow-up	Post-Challenge
Biochemistry (i)	X	X								X			X				X	(X)	X	X
Coagulation (i)	X																			
Cardiac enzymes	X	X											X				X			
Thyroid function test	X																			
Blood serum for humoral immunity (j)	X	X																	X	(X)
Blood – Pharmacokinetics (PK) (d)								(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		(X)
Blood – Proteomics (exploratory)		X						(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		(X)
Collection of Respiratory Samples																				
Nasopharyngeal swab - Respiratory pathogen screen (k)		X																		
Nasopharyngeal swab - Respiratory syncytial virus (RSV) discharge test (h)																	(X)	(X)		
Nasal sampling – Virology (polymerase chain reaction [PCR] & culture) (e, l)			X					2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X		
qualitative integrative cycler (qic) PCR assay for triggered dosing**								2X	2X	2X	X									
Safety Assessments																				
Adverse Events (AEs) (n)												X								
Concomitant medications (n)												X								

KEY NOTES FOR SCHEDULE OF EVENTS

(X)	The assessment may be optional, or at the discretion of the principal investigator (PI)/investigator.
X	Once daily, assessments conducted once during the 24-hour period.
2X	Twice daily, assessments conducted twice during the 24-hour period.
3X	Three times daily, assessments conducted 3 times during the 24-hour period.
*	Results of tests or examinations performed under hVIVO generic screening process may be used to determine eligibility without the need to repeat all assessment prior to inoculation with challenge agent. Hepatitis and HIV serology should be repeated on the first study day if outside of 56-days window. Screening assessments (including repeats, as required), may be performed up to Day -1 at the discretion of the PI/investigator and in accordance with the design of the study.
**	Assay to stop once a positive RSV result is obtained.
a	Study-specific consent may occur on the day of admission to the quarantine unit, providing all required eligibility information has been collected through the Health Research Authority approved hVIVO generic screening process.
b	Only the applicable inclusion/exclusion criteria will be reviewed at each time point.
c	Height will be measured at screening only.
d	Blood -Proteomics (Exploratory) Time points (hours) for pharmacokinetic (PK) sampling (in blood samples) are as follows: Dose 1: pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15 hours post-dose; Dose 2: pre-dose; Dose 3: pre-dose; Dose 4: pre-dose; Dose 5: pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60, 72 hours post-dose The allowable time windows for the sampling are as follows: • ± 5 minutes from the scheduled time for time points ≤ 2 hours from dosing • ± 15 minutes from the scheduled time for time points > 2 hours to ≤ 24 from dosing • ± 60 minutes from the scheduled time for time points > 24 hours to ≤ 48 from dosing • ± 2 hours from the scheduled time for time points > 48 hours from dosing There is no time window requirement for the pre-dose sample. The pre-dose sample must be taken prior to dose. Between Day 2 and Day 12 Proteomic (exploratory) blood samples will be collected after a PK sample at the following timepoints: Pre each Dose: (Dose 1 through to Dose 5) and post Dose 5 at 24, 48 and 72 hrs.
e	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 (SDC) baseline: The assessment(s) on Day -1 are considered as the baselines for the subsequent timing windows (assessments on Day -1 will be performed approximately 8 hours [±1 hour] apart). • Respiratory Infection Intensity and Impact Questionnaire (RiiQ) baseline: The assessment on Day -1 are considered as the baselines for the subsequent timing windows. Assessments will be performed once daily at the same time each day (± 1 hour from baseline) during quarantine. • Nasal sample baseline: The AM and PM samples on Day 2 are considered as the baselines for the subsequent AM or PM timing windows (assessments on Day 2 will be performed approximately 12 hours [±1 hour] apart). The above baseline requirements are based on an admission on Day -2, if participants are admitted to quarantine on Day -1, appropriate Day 0 time points may be used for baseline timings.
f	Distribution of paper tissues and collection bags will start in the morning on Day -1, with the first collection on Day 0. Thereafter, distribution and collection of tissues will occur daily, at the same time point (±1 hour) in the morning, with tissues distributed 24 hours ahead, until discharge from quarantine.
g	Randomization will take place prior to the first IMP dosing on the day of the first IMP dosing.
h	Viral discharge test (e.g., antigen test) is performed as required by the PI.
i	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).
j	Blood serum humoral markers assumes assays specific to the viral challenge agent (i.e., neutralization assay). Serosuitability will be determined from sample collected within 90 days before challenge virus inoculation.
k	Upper respiratory tract (URT) swab (e.g., nasopharyngeal 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.
l	Post inoculation nasal wash virology samples will be collected and used for quantitative reverse transcription-polymerase chain reaction (qRT-PCR) and viral culture assay (as appropriate). Samples collected between the morning of Day 2 and the morning of Day 5 will also be used for qualitative integrative cycler (qic) PCR until a positive result is received (to support triggered dosing). Samples may be used for related viral genomics and exploratory research.
m	IMP administration will be initiated (triggered) by a positive RSV result (measured by qicPCR) between Day 2 and Day 5 AM (nasal sampling twice daily, morning and evening; on Day 5 only in the morning). Dosing will start approximately 12 hours (±1 hour) after first detection of RSV. If no positive RSV result is obtained, dosing will start in the evening of Day 5. Duration of treatment with EDP-323 (or placebo) will be 5 days (once daily [QD], approximately 24 hours [±1 hour] apart), with the start day dependent on RSV result.

n	Adverse events (AEs) and concomitant medications are reviewed throughout the study.
o	Assessments performed on Day -2 may be performed on Day -1. For example, participants may be admitted to the quarantine unit on Day -2 or Day -1. If admitted on Day -1, Day -2 assessments will be performed on Day -1, as appropriate.
p	If some of the assessments required as part of the early withdrawal visit have already been performed as per the daily SoE, the completed assessments will not be repeated on the same day as part of early withdrawal visit, unless clinically indicated.
Notes:	• 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) sample collection:	**Yes**	☐	**No**	☒
Ribonucleic acid (RNA) sample collection	**Yes**	☐	**No**	☒
Proteomic sample collection	**Yes**	☒	**No**	☐
Consent considerations:	Genetic consent. Future use samples for exploratory research: a blood sample (up to 10 mL), nasal wicks, and nasal swabs for further exploratory "omics" analysis relevant to the main objectives of the study, but yet to be defined. Future use of remaining samples for new ethically approved health research and laboratory testing protocols, according to the local laws.			

2. INTRODUCTION

EDP-323 is a novel orally administered inhibitor of the L protein of respiratory syncytial virus (RSV). EDP-323 is being developed as a potential treatment for RSV infection.

2.1. Background

Respiratory syncytial virus is the most common cause of acute lower respiratory infection (ALRI) in infants and children (Bont et al, 2016; Hall et al, 2009; Nair et al, 2010). Globally, it was estimated in 2005 that RSV caused 33.8 million episodes of ALRI (~22% of all ALRI) and 3.4 million episodes of severe ALRI requiring hospitalization among children <5 years old worldwide (Nair et al, 2010). Mortality from RSV infection is significant, with an estimated 66,000 to 199,000 childhood deaths in 2005 worldwide (Nair et al, 2010). The overwhelming majority of these deaths occur in children below the age of 2 years and in developing countries (Bont et al, 2016; Nair et al, 2010). The most recent estimates of global RSV disease burden showed that, in 2015, there were no substantial changes in the number of new episodes of RSV-ALRI and related hospital admissions compared to 2005, but a lower number of in-hospital deaths (Shi et al, 2015). Moreover, for children younger than 6 months, Shi et al reported about 1.4 million hospital admissions and 27,300 in-hospital deaths due to RSV-ALRI in 2015 worldwide (Shi et al, 2015).

It should be noted that RSV is also increasingly being recognized as a significant cause of morbidity and mortality in older adults and those with underlying chronic cardiopulmonary disorders (Agius et al, 1990; Falsey et al, 1995). The risk of severe RSV disease is higher in the frail elderly and those with co-morbidities, including congestive heart failure, stroke, chronic kidney disease, chronic obstructive pulmonary disease, and immunosuppression. In the United States, RSV illness in adults >65 years old ranges from 3% to 7% annually, resulting in approximately 177,000 hospitalizations and 14,000 deaths.

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 DeVincenzo et al, 2020; DeVincenzo et al, 2022; Lambkin-Williams et al, 2018; Stevens et al, 2018) and vaccines (Bavarian Nordic 2021; Pfizer 2021; Sadoff et al, 2022). Specifically, hVIVO have safely and successfully used the RSV challenge strain in over 1,700 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 characterized 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.

2.2. Information about EDP-323

2.2.1. Product Description

EDP-323 is a potent and selective non-nucleoside inhibitor of the large protein (L protein) of RSV.

2.2.2. Nonclinical Studies

2.2.2.1. Drug Metabolism and Pharmacokinetics

Nonclinical studies have been conducted to characterize the pharmacokinetics (PK) of EDP-323 in CD-1 mice, Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys following a single intravenous and/or oral dose. In addition, multiple-dose oral PK studies were conducted in mice and monkeys. The mouse and the monkey were selected as the primary toxicology species to evaluate the safety of EDP-323.

Based on the outcome of the absorption studies, EDP-323 is projected to have good oral absorption in humans.

EDP-323 was shown to be stable in human liver microsomes, human hepatocytes, human intestinal S9, and human plasma No unique human metabolites have been observed to date.

2.2.2.2. Safety Pharmacology and Toxicology

Safety pharmacology studies demonstrated that EDP-323 was safe for respiratory, cardiovascular, and nervous systems at the studied doses.

EDP-323 was negative for mutagenicity in the in vitro Ames assay. EDP-323 was negative for clastogenicity in the in vivo bone marrow micronucleus assay . However, a positive response was observed in the long-term exposure -S9

condition in the GLP in vitro micronucleus assay (negative in the short-term exposures +/- S9). Thus, consistent with the International Council for Harmonisation (ICH) S2 (R1) (2011) weight of evidence approach, a second in vivo (comet) assay was conducted; EDP-323 was negative in CD 1 mice for DNA damage when dosed to the limit of the assay [redacted].

Refer to the EDP-323 Investigator's Brochure (IB) for further details of referenced nonclinical studies (IB, 2024).

2.2.3. Clinical Studies

EDP-323 was evaluated in a Phase 1, randomized, double-blind, placebo-controlled, first-in-human (FIH) study in which the safety, tolerability, and PK was assessed in healthy adult subjects. The Phase 1 study included a single ascending dose (SAD) phase enrolling a total of 6 dose cohorts [redacted] of which, one was a 2-part food effect (FE) cohort, and a multiple ascending dose (MAD) phase enrolling 4 dose cohorts [redacted]. All SAD and MAD cohorts enrolled 8 participants who were randomized to receive EDP-323 or placebo in a 3:1 ratio. The [redacted] SAD/FE cohort enrolled 10 subjects randomized in a 4:1 ratio.

As of October 2023 unblinded safety and PK data for all SAD and MAD cohorts are available. Overall, no safety concerns were reported in the [redacted] healthy subjects dosed orally with EDP-323 or placebo as single or multiple doses. EDP-323 was generally well tolerated at single doses [redacted] with 2 subjects reporting a total of 4 treatment-emergent adverse events (TEAEs). Of the 4 TEAEs reported during the SAD phase, [redacted] all were deemed not related or unlikely related to the study drug. One subject in the SAD/FE [redacted] cohort discontinued due to an TEAE of syncope (moderate; unlikely related to study drug). EDP-323/placebo was also well tolerated at multiple doses [redacted] for 7 days. Ten subjects reported a total of 13 TEAEs. [redacted] Ten of the 13 TEAEs were deemed unlikely or not related to EDP-323/placebo. Of the 3 TEAEs deemed possibly related to EDP-323/placebo, all were mild, with 2 headaches and 1 gastrointestinal (frequent stools) events. There were no discontinuations due to adverse events (AEs) in the MAD. In both the SAD and MAD phases, there were no serious AEs, serious adverse events (SAEs), clinically significant abnormal laboratory findings, vital signs, electrocardiograms (ECGs), or physical exam findings.

Based on preliminary PK data, EDP-323 was rapidly absorbed [redacted] following single and multiple dosing. EDP-323 exposure increased with increasing single and multiple dosing [redacted] with accumulation at Day 7 following QD multiple doses [redacted] No food effect was observed with a high fat meal during the [redacted] SAD FE cohort. [redacted]

In Summary:

- EDP-323 was well tolerated and generally safe over a broad range of single doses [redacted] and multiple doses [redacted] QD for 7 days.
- EDP-323 exhibited PK characteristics supporting QD dosing and can be administered without regard to food.

These results support further clinical evaluation of EDP-323 in patients with RSV.

For a detailed description of available clinical data, please refer to the EDP-323 IB (IB, 2024).

2.3. Study Rationale

The purpose of this Phase 2a study is to evaluate the safety, PK, and antiviral activity of multiple doses of orally administered EDP-323, compared to placebo, in a healthy adult participants inoculated with RSV-A Memphis 37b.

The RSV-A Memphis 37b challenge strain has been used for over 15 years by both hVIVO and others and has helped assess numerous RSV therapies. Specifically, hVIVO have safely and successfully used the RSV-A Memphis 37b challenge strain in over 1,700 healthy participants (18 to 60 years of age)], including the inoculation of 24 participants between 60 and 75 years of age.

2.4. Benefit/Risk Assessment

Healthy participants will not benefit from this clinical study. The study is designed to provide information about the antiviral effect, PK, and safety/ tolerability of EDP-323. Results from this clinical study will be useful in developing a new antiviral therapy for RSV.

Information about the known and expected benefits and risks and reasonably expected AEs of EDP-323 are highlighted in Section 2.2.3, Clinical Studies, and additional details may be found in the IB (IB, 2024).

2.4.1. Risk Assessment

The known risks to participants are detailed below. 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 minimized. Trained medical staff and appropriate facilities will be available to provide medical emergency care.

Potential Risk of Clinical Significance	Description of Risk	Mitigation Strategy
Study Intervention		
Oral administration of EDP-323 capsules	1. During FIH study EDP 323-001, EDP-323 was well tolerated at single and multiple doses [redacted] (QD). No safety concerns were identified. In both the SAD and MAD phases, there were no serious AEs, SAEs, clinically significant abnormal laboratory findings, vital signs, ECGs, or physical exam findings (see Section 2.2.3, Clinical Studies). 2. EDP-323 has not previously been tested in human subjects with RSV and may not confer any antiviral protection against RSV in humans despite encouraging preclinical evidence.	1. Participant safety data will be monitored throughout the study, including but not limited to physical exams, vital signs, 12-lead ECG, and clinical laboratory results. 2. Participants 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.
Oral administration of placebo capsules	Given that the placebo is a pharmacologically inert material, there should be no risk.	Not applicable.
Study Procedures		
Intravenous catheter	The primary risks of the placement of an intravenous catheter include local discomfort, occasional bleeding or bruising of the skin at the site of the needle puncture, hematoma, and rarely, infection or fainting.	The participant will be closely monitored and asked about these symptoms before being allowed to stand up.
Blood sampling	Pain or bruising at the site where blood is drawn.	Blood samples will be obtained by a trained professional.
	Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle insertion.	Blood samples will be obtained by a trained professional and procedures will be put in place to avoid injury from fainting.

Potential Risk of Clinical Significance	Description of Risk	Mitigation Strategy
	There is a possibility that in the process of collecting blood a nerve may be injured.	Procedure to be performed by qualified study staff.
	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 (e.g., human immunodeficiency virus [HIV] or hepatitis) or an unexpected illness.	If the infection is clinically significant and affects the participant psychologically or physically, this will be discussed with the participant and advice will be given accordingly. 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 (e.g., nasopharyngeal swabs) may cause discomfort, sneezing, watery eyes, irritated nose, or nose bleeding.	Sample collection will be performed by appropriately qualified and trained study staff to minimize 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. 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-	The safety profile of the RSV-A Memphis 37b is well characterized in healthy adults as this has been used for over 15 years by hVIVO. At hVIVO more than 1,700 healthy adults aged 18 to 60 years have been challenged with the RSV challenge strain. 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.

Potential Risk of Clinical Significance	Description of Risk	Mitigation Strategy
	related myocarditis rarely, with symptomless occurrences likely going undiagnosed in the community. Within our RSV viral challenge studies, of over 1,700 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.	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 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 1,700 inoculations. As appropriate, the principal investigator (PI)/delegate may request additional testing of nasal swab samples using a qualitative virus antigen test or polymerase chain reaction (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 Section 2.4.1.1, Vulnerable Persons, for 2 weeks after they leave the quarantine unit.

Potential Risk of Clinical Significance	Description of Risk	Mitigation Strategy
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 viral 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. If a participant develops 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 and dependent on medical history, will be referred to their GP or any specific department at hospital, as required.
Lower infection rate / disease than assumed	If a lower number of participants become infected than expected there is a risk the study could be underpowered to detect a difference between placebo and EDP-323.	A designated, blinded team may be employed to monitor the infection rate while the study is ongoing to assess if additional participants are needed to be enrolled. If performed, the recommendation of the infection rate monitoring will be reviewed by the sponsor and investigator to consider if additional participants are needed to be enrolled.
Consult the Investigator's Brochure (IB) for detailed information on EDP-323 (IB, 2024)		

2.4.1.1. Vulnerable Persons

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

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

2.4.1.2. Risk Associated With Coronavirus Disease 2019 Pandemic

hVIVO has implemented enhanced infection control measures during the pandemic to minimize risks of coronavirus disease 2019 (COVID-19) infection.

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

It has not been established that severity of COVID-19 infection could increase if contracted after inoculation with 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 EDP-323 administration.

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

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

2.4.2. Benefit Assessment

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

Participants may develop some immunity to RSV-A Memphis 37b virus and benefit from a general health check at screening. Benefit may also be derived from the medical evaluations and assessments associated with study procedures. In addition, participants are contributing to the process of developing new therapies in an area of unmet medical need.

2.4.3. Overall Benefit/Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with EDP-323 and challenge virus administration are justified by the anticipated benefits linked to the evaluation of EDP-323 in a viral challenge model in healthy adults, which will subsequently facilitate future development of antiviral RSV therapies.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	
Efficacy	
• To evaluate the antiviral activity of EDP-323 compared to placebo in healthy adult participants inoculated with RSV-A Memphis 37b	• Reduction in RSV area under the viral load-time curve (VL-AUC) measured by quantitative reverse transcription-polymerase chain reaction (qRT-PCR) in nasal samples
Secondary:	
Efficacy	
• To further evaluate the antiviral activity of EDP-323 compared to placebo in healthy adult participants inoculated with RSV-A Memphis 37b • To evaluate the clinical disease severity in healthy adult participants inoculated with RSV-A Memphis 37b followed by administration of EDP-323 compared to placebo	• Viral load: o RSV viral load by qRT-PCR of nasal samples including: • Reduction in RSV peak viral load (VLPEAK) • Reduction in time to RSV VLPEAK after first dosing • Time to RSV viral load negativity after first dosing • Time to first negative slope of RSV viral load after first dosing • Slope of the RSV viral load over time (clearance rate) from time of RSV VLPEAK to 1, 2, 3, and 4 days later o RSV viral load by cell culture (plaque assay) of nasal samples, including: • Reduction in RSV VL-AUC • Reduction in RSV VLPEAK • Reduction in time to RSV VLPEAK after first dosing • Time to RSV viral load negativity after first dosing • Time to first negative slope of RSV viral load after first dosing • Slope of the RSV viral load over time (clearance rate) from time of RSV VLPEAK to 1, 2, 3, and 4 days later

Objectives	Endpoints
	• Clinical symptoms and disease severity: o Effect on RSV symptoms using the symptom diary card [SDC]), with endpoints including: • Reduction in area under the total symptom score (TSS)-time curve (TSS-AUC) • Reduction in peak TSS • Time to return to baseline (last assessment before RSV inoculation) TSS • Reduction in time to peak TSS o Total weight of nasal discharge (mucus) produced o Total number of tissues used
Pharmacokinetics	
• To evaluate the PK profile of EDP-323 (and metabolites) in blood samples in healthy adult participants inoculated with RSV-A Memphis 37b • To characterize the relationship between plasma PK of EDP-323 and VL-AUC (qRT-PCR) and TSS-AUC in healthy adult participants inoculated with RSV-A Memphis 37b	• EDP-323 (and metabolites) concentrations and PK parameters in blood samples: maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), apparent systemic clearance (CL/F), terminal elimination rate constant (λ_z), volume of distribution (Vd/F), plasma concentration at 12 hours (C_{12h}), plasma concentration at 24 hours (C_{24h}), area under the concentration-time curve from time 0 to time of last quantifiable concentration (AUC_{last}), area under the concentration-time curve over the dosing interval ($AUC_{0\text{-}tau}$), and area under the concentration-time curve from time 0 to infinity ($AUC_{0\text{-}\infty}$), and other parameters as applicable • EDP-323 plasma PK (area under the curve [AUC]) correlations with VL-AUC (e.g., qRT-PCR) and TSS-AUC
Safety	
• To evaluate the safety of EDP-323 in healthy adult participants inoculated with RSV-A Memphis 37b	• Occurrence of AEs from initial administration of investigational medicinal product (IMP) up to discharge • Occurrence of AEs from initial administration of IMP up to Day 28 follow-up • Occurrence of SAEs from initial administration of IMP up to Day 28 follow-up

Objectives	Endpoints
[redacted]	
[redacted]	
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overview of Study Design

This is a randomized, Phase 2a, double-blind, placebo-controlled study to evaluate the safety, PK, and antiviral activity of multiple doses of orally administered EDP-323 against RSV infection in healthy adults after challenge with RSV-A Memphis 37b.

In this study, 2 doses of EDP-323 will be tested: EDP-323 high dose (600 mg QD for 5 days) vs low dose (600 mg loading dose for 1 day followed by 200 mg QD for 4 days). The study will have a placebo arm. Due to its exploratory nature, no adjustment will be made to the type 1 error in this proof-of-concept study.

The expected duration of study participation for a participant is up to 4 months, from screening to the participant's last scheduled follow-up visit, with the following sequence and duration of study phases:

Screening:

- Screening prior to inoculation with challenge virus from Day -90 to Day -2/-1.

  Results of tests or examinations performed under hVIVO generic screening process may be used to determine eligibility without the need to repeat all assessment prior to inoculation with challenge agent. Hepatitis and HIV serology should be repeated on the first study day if outside of 56-days window. Screening assessments (including repeats, as required), may be performed up to Day -1 at the discretion of the PI/investigator and in accordance with the design of the study.

Inpatient Phase:

- Participants will be resident in the quarantine unit for approximately 15 days, from admission on Day -2/-1 to planned discharge on Day 12. Discharge from quarantine is foreseen at Day 12 if the participant has no clinically significant symptoms. The detection of virus by RSV discharge test (e.g., qualitative rapid viral antigen test [RVAT]) will be performed at investigator's discretion. If the participant continues to have clinically significant symptoms, additional extended quarantine stay may be required based on the assessment of the PI/investigator.

Procedures will include:

- **Pre-human Viral Challenge**:
  - Admission to quarantine unit on Day -2/-1.
  - Baseline assessments will be conducted as per SoE up to Day 0, pre-challenge.
- **Human Viral Challenge**:
  - RSV-A Memphis 37b virus inoculation on Day 0.
- **Post-human Viral Challenge**:
  - Randomization to receive EDP-323 or matched placebo.
  - Administration of IMP (EDP-323 or placebo). IMP administration will be initiated (triggered) by a positive RSV result (measured by qualitative integrative cycler [qic] PCR) between Day 2 and Day 5 AM (nasal sampling twice daily, morning and evening; on Day 5 only in the morning).

Dosing will start approximately 12 hours after first detection of RSV. If no positive RSV result is obtained, dosing will start in the evening of Day 5. Duration of treatment with EDP-323 (or placebo) will be 5 days (QD) in the period from Days 2 to 9, with the start day dependent on RSV result.

- Day 1 onwards and each day – study assessments will be conducted as per SoE.
- Discharge from quarantine is planned on Day 12 post inoculation.

Outpatient Phase:

- Follow-up visit: Day 28 (±3 days)

*Following challenge agent inoculation, participants will be closely observed for 24 hours, specifically for potential allergic reactions and any AEs. Post inoculation, participants will lie flat for 10 minutes, then sit up with nose pegs on for 20 minutes. Participants will continue to be monitored throughout the clinical phase of the study.

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 1,700 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 specialized clinical facilities in a quarantine unit. 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 Randomization

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 EDP-323.

Randomization will be used to prevent bias in the assignment of participants to treatment groups (EDP-323 or placebo), to increase the likelihood that known and unknown participant characteristics (e.g., demographic and baseline characteristics) are equally balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

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

Together, the placebo-controlled, randomized, and blinded features of the study will allow a causal interpretation of the study results.

4.3. Justification for Dose

EDP-323 will be administered orally. The doses selected for the study are as follows:

- High dose: 600 mg EDP-323 QD for 5 days

- Low dose: 600 mg EDP-323 (loading dose) for 1 day, followed by 200 mg EDP-323 QD for 4 days

These doses are expected to provide exposures in the anticipated therapeutic range. In the [redacted] EDP 323-001, EDP-323 exposure increased with increasing dose [redacted] in both the SAD and MAD phase. Single EDP-323 doses [redacted] were safe and well tolerated (Section 2.2.3, Clinical Studies). Based on preliminary PK [redacted] systemic exposures [redacted] supporting QD dosing. In the MAD phase, where EDP-323 was administered QD for 7 days, doses [redacted] were safe and well tolerated (Section 2.2.3, Clinical Studies). Available PK data from multiple-dose cohorts indicate that there was accumulation at Day 7 [redacted] following daily dosing for 7 days, [redacted]

Based on in vitro testing, a protein adjusted 90% effective concentration (EC_{90}) value for EDP-323 [redacted] was determined using primary human airway epithelial cells grown at an air liquid interface (3D pHAEC-ALI). [redacted] based on exposures from the FIH study, these doses are expected to provide mean exposures approximately 33-fold over the free drug EC_{90} in 3D pHAEC-ALI 24 hours after Day 1 for both dose levels, and 44-fold and 11-fold after dosing on Day 5 at the high and low dose, respectively.

4.4. 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 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** **Final v5.0_19OCT2022 (Viral Challenge Volunteer Studies)**
To be eligible for the study, participants must meet all the following inclusion criteria:	
1	Written informed consent signed and dated by the participant and the Investigator obtained before any assessment is performed
2	Aged between 18 and 55 years 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 ≤35 kg/m^2.
4	In good health with no history, or current evidence, of clinically significant medical conditions, and no clinically significant test abnormalities 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: i. Postmenopausal females defined as amenorrhea for 12 months or greater with no alternative medical cause. A high follicle-stimulating hormone (FSH) level, within appropriate postmenopausal range, may be used to confirm postmenopausal state in the absence of combined hormonal contraception or hormone replacement therapy. If there is less than 12 months of amenorrhea 2 FSH samples are required at least 4-6 weeks apart. ii. Documented status as being permanently sterile (e.g., tubal ligation, hysterectomy, bilateral salpingectomy, and bilateral oophorectomy).

No.	**hVIVO APPROVED STANDARD INCLUSION CRITERIA** **Final v5.0_19OCT2022 (Viral Challenge Volunteer Studies)**
To be eligible for the study, participants must meet all the following inclusion criteria:	
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 2 weeks prior to the first study visit. The contraception use must continue until 90 days after the date of last dosing with IMP. Highly effective contraception is as described below: a. Established use of hormonal methods of contraception described below (for a minimum of 2 weeks 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 (estrogen 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 sterilization (with the appropriate post vasectomy documentation of the absence of sperm in the ejaculate) where the vasectomized 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 date of last dosing with IMP: a. Use a condom with a spermicide to prevent pregnancy in a female partner or to prevent exposure of any partner (male and female) to the IMP.

No.	hVIVO APPROVED STANDARD INCLUSION CRITERIA Final v5.0_19OCT2022 (Viral Challenge Volunteer Studies)
To be eligible for the study, participants must meet all the following inclusion criteria:	
	b. Male sterilization 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 trial and the preferred and usual lifestyle of the participant. c) In addition to the contraceptive requirements above, male participants must agree not to donate sperm following discharge from quarantine until 90 days after the date of last dosing with IMP.
8	Serosuitable for the challenge virus. • The serology result obtained from the RSV antibody assay suggests that the participant is sensitive to RSV 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 Final v5.0_19OCT2022 (Viral Challenge Volunteer Studies)
Participants who meet any of the following exclusion criteria will not be included in the study:	
Medical History	
1	History of, or currently active, symptoms or signs suggestive of upper or lower respiratory tract (URT or LRT) infection within 4 weeks prior to the first study visit.
2	Any history or evidence of any clinically significant or currently active cardiovascular, respiratory, dermatological, gastrointestinal, endocrinological, hematological, hepatic, immunological (including immunosuppression), metabolic, urological, renal, neurological, or psychiatric disease and/or other major disease that, in the opinion of the PI/investigator, may interfere with a participant completing the study and necessary investigations. The following conditions apply:

No.	**hVIVO APPROVED STANDARD EXCLUSION CRITERIA** **Final v5.0_19OCT2022 (Viral Challenge Volunteer Studies)**
Participants who meet any of the following exclusion criteria will not be included in the study:	
	a) Participants with a history of resolved depression and/or anxiety may be included at the discretion of the PI. Participants with a history of stress related illness, which is not ongoing or requiring current therapy, with good evidence of preceding stressors may also be included at the PI's discretion. As required, participants will be assessed prior to enrolment with a Patient Health Questionnaire (PHQ-9) and/or Generalized Anxiety Disorder Questionnaire (GAD-7) which must score less than or equal to 4 on admission. b) Rhinitis (including hay fever) which is clinically active or a history of moderate to severe rhinitis, or history of seasonal allergic rhinitis likely to be active at the time of inclusion into the study and/or requiring regular nasal corticosteroids on an at least weekly basis, within 30 days of admission to quarantine will be excluded. Participants with a history of currently inactive rhinitis (within the last 30 days) or mild rhinitis may be included at the PI's discretion. c) Atopic dermatitis/eczema which is clinically severe and/or requiring moderate to large amounts of daily dermal corticosteroids will be excluded. Participants with mild to moderate atopic dermatitis/eczema, taking small amounts of regular dermal corticosteroids may be included at the PI's discretion. d) Any concurrent serious illness including history of malignancy that may interfere with a participant completing the study. Basal cell carcinoma within 5 years of initial diagnosis or with evidence of recurrence is also an exclusion. e) Participants reporting physician diagnosed migraine can be included provided there are no associated neurological symptoms such as hemiplegia or visual loss. Cluster headache/migraine or prophylactic treatment for migraine is an exclusion. f) Participants with physician diagnosed mild irritable bowel syndrome (IBS) not requiring regular treatment can be included at the discretion of the PI.
3	Any participants who have smoked ≥10 pack years at any time (10 pack years is equivalent to one 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.

No. **Participants who meet any of the following exclusion criteria will not be included in the study:**	
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 hospitalized due to epistaxis on any previous occasion. c) Any nasal or sinus surgery within 3 months prior to the first study visit.
Prior or Concomitant Medications and Assessments	
8	a) Evidence of vaccinations within the 4 weeks prior to the planned date of viral challenge. b) Intention to receive any vaccination(s) before the last day of follow-up. (NB. No travel restrictions will apply after the Day 28 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 human viral challenge 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:

No. **Participants who meet any of the following exclusion criteria will not be included in the study:**	
	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 known to be potent inducers or inhibitors of cytochrome P450 enzymes or P-glycoprotein, 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 g paracetamol over the preceding week) d) Systemic antiviral administration within 4 weeks prior to viral challenge.
12	a) Confirmed positive test for drugs of abuse and cotinine on first study visit. One repeat test allowed at PI discretion. b) Recent history or presence of alcohol addiction, or excessive use of alcohol (weekly intake in excess of 28 units alcohol; 1 unit being a half glass of beer, a small glass of wine or a measure of spirits), or excessive consumption of xanthine-containing substances (e.g., daily intake in excess of 5 cups of caffeinated drinks e.g., coffee, tea, cola).
13	A forced expiratory volume in 1 second (FEV1) <80%.
14	Positive HIV, hepatitis B, or hepatitis C test.
15	Presence of fever, defined as participant presenting with a temperature reading of ≥37.9 ºC on Day -2, Day -1, and/or pre-challenge on Day 0.
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 PI/investigator, would interfere with or serve as a contraindication to protocol adherence or the assessment of safety (including reactogenicity) will deem the participant unsuitable for the study. Any other reason that in the opinion of the PI/investigator raises a concern that the participant 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 fasting period from 0.5 hour pre-dose to 1 hour post-dose applies. No fluid intake (including water) is allowed for 1 hour pre-dose to 1 hour post-dose, except for the water used for IMP intake.

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 SDC.

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.

5.3.4. Other Restrictions

Participants will be instructed to avoid close contact with vulnerable people as described in Section 2.4.1.1, Vulnerable Persons, for 2 weeks after they leave the quarantine unit.

5.4. Screen Failures

Screen failures are defined as participants who sign the study-specific inform consent form (ICF) but are not subsequently enrolled into the study. Screen failures will not be included in the study database. 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 INTERVENTIONS AND CONCOMITANT THERAPY

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.

6.1. Study Intervention(s) Administered

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

Table 6-1: Study Interventions

Intervention Name	**EDP-323**	**Placebo**	**RSV-A Memphis 37b virus**
Type	Drug	Other	Challenge Virus
Formulation	Oral capsule	Oral capsule	Capped vial, liquid
Unit Dose Strength(s)	[redacted]	Not applicable	The challenge agent titer is determined in an infectivity assay. The dose is approximately 4 $\log_{10}$ plaque-forming units (PFU)
Dosage Level(s)	• High dose: 600 mg EDP-323 QD for 5 days • Low dose: 600 mg EDP-323 (loading dose) for 1 day, followed by 200 mg EDP-323 QD for 4 days	Not applicable	A single dose of challenge agent will be delivered
Route of Administration	Oral	Oral	Intranasal
Use	IMP, experimental	IMP, placebo	Infectious challenge agent
Sourcing	Provided by sponsor	Provided by sponsor	Provided centrally by hVIVO
Packaging and Labelling	The details of the packaging and labelling	The details of the packaging and labelling	The details of the challenge agent

Intervention Name	EDP-323	Placebo	RSV-A Memphis 37b virus
	will be provided in the study-specific pharmacy manual	will be provided in the study-specific pharmacy manual	provision will be provided in the analytical plan (AP)
Current/Former Name(s) or Alias(es)	Not applicable	Not applicable	Not applicable

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Investigational Medicinal Product

hVIVO will receive EDP-323 [redacted] oral capsules and placebo to match EDP-323 [redacted] oral capsules to be storage at [redacted] after the supply has received qualified person sign off by the Good Manufacturing Practice (GMP) sponsor's representative/pharmacy provider and has been released for shipment. All IMP supplies will be used only for this protocol and for no other purpose.

Ready-to-dispense IMP will be supplied to hVIVO at the beginning of the study. Once received at hVIVO, hVIVO study staff will perform stock level accountability and the IMP will be stored securely. 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 condition 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.

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. 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 -60°C to -90°C).

Inoculum vials containing the challenge agent will be prepared and/or provided according to the hVIVO analytical plan (AP). The inoculum will be administered intranasally to each participant 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.

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 authorized 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 authorized investigator site staff.

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

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

6.3. Randomization and Blinding

6.3.1. Randomization

hVIVO assigns a unique number to each subject in the hVIVO database. This number will be used to identify a subject up to the point of randomization, on source documents, on all study correspondence, and in the study database. A separate randomization number will be allocated to the participants at randomization and will be used for allocation to a study arm.

A designated unblinded statistician, separate from the conduct or analysis of the study, will be responsible for the computer-generated randomization schedule using SAS.

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

Randomization numbers will follow a 4 digit format, e.g., [rnnn], where r will represent a replacement participant (0 by default, incremented by 1 for a replacement participant) and nnn will be incremental (e.g., 1 to 132).

In this study, 132 participants will be randomized 1:1:1 into one of 3 treatment groups (n=44 each) to receive EDP-323 (at 2 different doses) or placebo.

If participants are replaced as per Section 7.4, Participant Replacement Strategy, the replacement participant will be assigned a new, unique randomization number. The replacement participant will receive the same allocated, blinded treatment as the participant who is being replaced.

6.3.2. Blinding

Each participant will be dispensed blinded study intervention which is labelled with his/her unique randomization number throughout the study.

Due to the differing treatment regimens being tested, all participants will receive the same number of capsules. Participants will have their regimen supplemented by the administration of a placebo matched to EDP-323 in order to mimic the same number of capsules.

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

Individual access to a secured interactive web response system (IWRS) will be provided to the PI/investigator. The website, compliant with 21CFR part 11 guidelines, will be used if unblinding is necessary. In case of an emergency, the PI/investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. The blind should only be broken where knowledge of the IMP received is required to provide appropriate patient care. Participant safety must always be the first consideration in making such a determination. If the PI/investigator decides that unblinding is warranted, the PI/investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. When the PI/investigator breaks the code, he/she will have to indicate on the website the reason for unblinding. The person who performed the unblinding and the date of time of code breaking will be automatically recorded. After confirmation, the nature of treatment will appear on the screen. A notification with the nature of treatment will also be provided by email. A notification, without the nature of treatment, will be provided to the study team. The PI/investigator must notify the sponsor within 24 hours that the code has been broken.

Even if the code is broken, blood samples for safety, efficacy, PK, and other assessments will continue to be drawn for the remainder of the planned study period following the last dose if doing so will not compromise participant welfare.

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

Participants 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.

Concomitant therapies and procedures related to the treatment or diagnosis of an AE will be recorded in the source data.

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 other than contraceptives 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
Vaccinations	4 weeks prior to planned date of viral challenge up through the last day of follow-up
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 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 or P-glycoprotein
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 program 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 any drug administered as part of the study greater than the dose prescribed by the protocol will be considered an overdose.

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

1. Contact the 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 within 24 hours of the date/time of the last dose of study intervention.
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 Medicines and Healthcare Regulatory Agency (MHRA) and Research Ethics Committee (REC) of the potential serious breach within 7 days of becoming aware of it.

7. WITHDRAWAL/DISCONTINUATION OF STUDY INTERVENTION

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 conducted, 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.

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.

Participants will be counselled that an early self-discharge or their withdrawal from the human viral challenge 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 an early self-discharge or 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 2.4.1.1, Vulnerable Persons.

The participant's consent to continue or not in the study and any requirement to attend further scheduled follow-up visits will be discussed, confirmed, and documented. If consent is not being withdrawn, assessments (early withdrawal visit assessments as detailed in the SoE), may still be collected, as clinically required, prior to the early discharge. Scheduled follow-up visits may be attended as agreed or for safety reasons. Any missed assessments or follow-up visits i.e., a missed PK timepoint will be documented as a protocol deviation.

7.2. Participant Discontinuation

Participants will be discontinued from further study intervention (i.e., receipt of the challenge agent or IMP as applicable) or withdrawn from the study for any of the reasons listed below. Where IMP has been administered, these participants must not receive any additional IMP but should continue to be followed for safety.

- 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 receipt of intervention or 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 or receipt of intervention would be in the participant's best interest.

- Termination of the study at the discretion of the PI/investigator or sponsor for safety, behavioral, 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).

Participants who are discontinued from further receipt of intervention (IMP) may undergo additional assessments or visits as necessary for safety reasons. If the participant is not withdrawing their consent, assessments as per the early withdrawal visit (see SoE) may still be collected if clinically required. Scheduled follow-up visits may also be attended as per 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 first study visit or 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 PI/investigator and sponsor. The replacement participant will receive the same intervention as the participant being replaced. The replacement participant will be assigned a new, unique

randomization number. The replacement participant will receive 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 unsuspected serious adverse reactions (SUSARs) during the study and the procedures that should be performed in each case are presented in Table 7-1.

Table 7-1: Study Stopping Rules

Status	Criterion	Procedure
1.	A 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.	
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, stabilization, 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 utilize 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 randomized for inclusion, and dosed/challenged: a. In an ongoing quarantine cohort b. In a new quarantine cohort c. Separately. 3. Any quarantine cohort may run at the same time	1. The stopping rules of the study must be always adhered to. Replacement participants may be enrolled to replace participants who have been withdrawn from the study for reasons not related to AEs, where the study stopping rule has not been met. 2. Due to considerations of the protocol specific participant replacement strategy, infection rate monitoring, and other rare occurrences, the number of study participants will not exceed 150 dosed with EDP-323/placebo. 3. Replacement participants will be given replacement randomization numbers (see Section 7.4, Participant Replacement Strategy). 4. All protocol-defined inclusion/exclusion criteria and safety criteria must be met before any study quarantine 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.

Adaptive Design Category	Feature	Limit
Duration of Inpatient Stay	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 suitability for residential stay will be assessed on a case-by-case basis. As such, a maximum length of stay cannot be prospectively defined.

8. STUDY ASSESSMENTS AND PROCEDURES

Unless otherwise stated, study assessments will be performed according to hVIVO SOPs. Study procedures and their timing are summarized 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 utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the period 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 Site File, and the Trial Master File.

8.1. Demographics and Baseline Characteristics

8.1.1. Demographics

Demographic data will be recorded at the screening visit.

8.1.2. Height, Body Weight, and Body Mass Index

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

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

8.1.3. Medical and Medication History

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

8.1.4. Challenge Agent Serology Samples

A participant must be serosuitable 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 titer cut-off for serosuitability will be described in the applicable hVIVO policy.

Serum levels of pre-existing RSV-specific antibodies will be determined using RSV challenge virus neutralization assay as described in the AP.

8.1.5. Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7) 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.

8.2. Respiratory Samples

The following exploratory nasal sampling procedures will be performed during the study and are detailed in the sections below:

- Nasopharyngeal swab
- Nasal wash

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

8.2.1. Nasopharyngeal Swab

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

- Respiratory pathogen screen
- RSV discharge test

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

8.2.1.1. Respiratory Pathogen Screen

On entry to quarantine, a nasopharyngeal swab will be collected and tested to detect the presence of a set of respiratory pathogens, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that could potentially contraindicate a person's participation in the study. Nasopharyngeal swabs will be tested using a multi-respiratory panel. Additional nasopharyngeal swabs may be collected if the results from the first test were invalid to support study eligibility prior to challenge agent inoculation, or if a community acquired infection is suspected during quarantine.

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

8.2.1.2. RSV Discharge Test

Where required, a RSV discharge test (e.g., qualitative rapid viral antigen test [RVAT]) will be used to determine the presence of RSV in a nasopharyngeal swab sample taken prior to discharge from the quarantine unit. A PCR test may be used as an alternative test for this purpose, details of which will be documented in the AP. The RSV discharge test will be performed at the discretion of the PI/investigator and only if indicated for a clinical or other reason. Additional tests may be performed at the discretion of the PI/investigator.

8.2.2. Nasal Wash

Nasal wash sampling will be performed to collect samples of nasal material for:

- Viral shedding/load assessments (see Section 8.3.3, Viral Load Assessment)
- Exploratory purposes (see Section 8.3.4, Exploratory Assessments)
- Biomarkers (see Section 8.10, Biomarkers)

Remaining material from the nasal wash may be stored and used for exploratory purposes in accordance with the AP.

8.2.3. Viral Shedding for Dosing

Viral shedding for triggered dosing decisions only will be confirmed by qicPCR assay of nasal wash sample.

8.3. Efficacy Assessments

8.3.1. Participant Diary Cards

Symptom Diary Card (Ordinal)

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 SDC. This information will be administered using paper and transcribed into the eCRF.

The following symptoms in the 13-item symptom questionnaire will be graded on a scale of 0 to 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 SDC, a visual analogue scale diary card using a 100 mm scale, with the same symptoms, will be completed by the participants.

Participant Common Cold Perception Questions

Two additional common cold-related questions will be answered by the participant each morning. The first question asks the participant's perception of whether they have a cold or not, the second asks the participant's perception of improvement/worsening of the cold.

1. Do you have a cold: Yes/No

If the participant selects Yes to having a cold, then the second 7-point Likert scale "global change since yesterday" question is completed by the participant, as below:

2. Compared to yesterday, I feel that my cold is:
    - Very much better
    - Somewhat better
    - A little better
    - The same
    - A little worse
    - Somewhat worse
    - Very much worse

Respiratory Infection Intensity and Impact Questionnaire (RiiQ)

Participants will report and assess the severity of their infection once daily during quarantine, at the same time each day (±1 hour), using the RiiQ (Romano et al, 2023). The RiiQ is a patient-reported outcome tool in development for assessing the severity of naturally-acquired RSV infection of adults. Participants will complete the RiiQ as per provided instructions. The RiiQ will be administered using paper and transcribed into the eCRF. It consists of a questionnaire addressing approximately 7 RSV symptoms, and 2 impacts of RSV (emotional and activity impacts). The multiple individual questions within the RiiQ are answered on a 4-point severity scale.

8.3.2. 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 in the morning on Day -1, with the first collection on Day 0. Thereafter, distribution and collection of tissues will occur daily, at the same time point (±1 hour) in the morning, with tissues distributed 24 hours ahead, until discharge from quarantine.

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

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

8.3.3. Viral Load Assessment

Viral load will be determined by qRT-PCR and a viral culture assay to investigate the following parameters:

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

[redacted]

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 SDC 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 in supine position, after being supine for at least 5 minutes.

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.

[redacted]

- Blood pressure (BP): systolic BP and diastolic BP will be measured in millimeters of mercury (mmHg). 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 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 recorded in supine position, after being supine for at least 5 minutes.

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 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 misuse and cotinine using commercially available kits that provide an instant result, which will be documented in the source data.

Drugs of misuse 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 Assessments and Analysis

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

8.4.6. 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 beta-human chorionic gonadotrophin (β-hCG) on admission to quarantine.

Blood samples will be tested for serum FSH in all postmenopausal female participants.

8.4.7. 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 (ATS/ERS) 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 repeated at any time in the event of respiratory signs or symptoms (repeated coughing, bradypnea, tachypnoea, rales, and rhonchi) or respiratory difficulties.

8.5. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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. For subjects who are not enrolled into the study, AEs will only be recorded in the source documents and SAEs should be reported to sponsor.

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), stabilization, 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 IB 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, fetal distress, fetal death, stillbirth, congenital anomaly/birth defect, ectopic pregnancy) are considered SAEs.

8.6. Pharmacokinetics

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

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 will be collected for measurement of plasma concentrations of EDP-323 (and metabolites) as specified in the SoE.

Blood plasma samples for measurement of plasma concentrations of EDP-323 (and metabolites) will be processed and sent to the sponsor's PK vendor according to the AP.

At the PI's discretion, blood samples 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.

Samples will be used to evaluate the PK of EDP-323 (and metabolites). Samples collected for analyses of EDP-323 (and metabolites) plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.6.2. Pharmacokinetic Parameters

Pharmacokinetic parameters of interest may include but are not limited to:

- C_{max}, t_{max}, $t_{1/2}$, CL/F, λ_z, Vd/F, C_{12h}, C_{24h}, AUC_{last}, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}\infty}$

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

8.7. Pharmacodynamics

Pharmacodynamic parameters may be evaluated in this study.

8.8. Immunogenicity Assessments

Aliquot(s) of blood (serum) will be collected for immunological analysis.

Humoral immune responses, e.g., RSV-neutralizing antibodies, will be evaluated from serum samples collected from all participants at the end of the study to evaluate the generation of natural immunity to the challenge virus with and without EDP-323 treatment, in accordance with the AP.

8.9. Genetics

Participant human genetics are not evaluated in this study.

8.10. Biomarkers

In addition to the planned blood plasma sample taken specifically for protein biomarker analysis, other serum and respiratory secretion samples may have their residual volumes aliquoted and stored for analysis as described in the AP. These aliquots may be used for protein biomarker analyses evaluating protein signatures and their correlations with disease severity, viral load, viral dynamics, and effects of EDP-323. Where aliquots are to be used for protein biomarker analyses, these samples will be sent to a sponsor-designated laboratory (or hVIVO where applicable) for such analysis in accordance with the AP.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary statistical hypothesis is that treatment with EDP-323 will show an antiviral effect demonstrated by a significant reduction in RSV VL-AUC (measured by qRT-PRC in nasal samples) compared to placebo.

9.2. Sample Size Determination

The statistical powering selected for this study is estimated to be sufficient for the primary objective and the primary endpoint and important secondary endpoints.

The sample size was calculated based on the assumptions of a 55% reduction in qRT-PCR VL-AUC, with a 72% coefficient of variation (CV) (based on similar previous studies), for a power of 80% and a 2-sided 5% level of significance (without adjustment for multiple comparisons) and assuming a 70% infectivity rate (based on similar previous studies). On this basis, it is estimated that 31 evaluable RSV infected (intent-to-treat infected [ITT-I]) participants per arm and 44 inoculated participants would be sufficient for the study to demonstrate an antiviral affect as measured by qRT-PCR with a power of at least 80% (achieved power computed as 84.1%). However, with the more conservative assumption of a 63% infection rate, 44 recruited participants, resulting in 24 infected participants would allow to detect a 55% relative reduction in qRT-PCR VL-AUC with at least 80% (81.0%) power.

The sample size of 44 participants per arm would allow to detect a decrease of 75% in TSS-AUC (CV of 92.9%) and 55% in TSS peak score (CV of 68.8%) with more than 80% power (87.8% and 87.2% respectively) assuming an infection rate of 70% (31 infected participants). The more conservative assumption of a 63% infection rate (28 infected participants) would allow to detect a 75% relative reduction in TSS-AUC and 55% in peak-AUC with respectively 84.3% and 83.6% power.

9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined (Table 9-1).

Table 9-1: Analysis Sets

Participant Analysis Set	Description
Enrolled	A participant will be considered as enrolled into the study once he/she has been inoculated with the challenge virus.
Intent-to-treat (ITT) analysis set	All participants having received challenge virus, randomized, and having received at least one dose of IMP.
Intent-to-treat infected (ITT-I) analysis set	All participants having received challenge virus, randomized, and having received at least one dose of IMP, and meeting the criterion for laboratory-confirmed RSV infection (see below for definition of laboratory-confirmed RSV infection). The ITT-I analysis set will be considered the primary analysis population for efficacy endpoints. A participant will fulfil the criteria for laboratory-confirmed RSV infection if:

Participant Analysis Set	Description
	• At least 2 positive detections by viral load qRT-PCR assay specific for the challenge virus, reported within 2 consecutive study days. and/or • One positive detection by viral load qRT-PCR assay, specific for the challenge virus, in which an aliquot of the same sample has also tested positive in a cell-based infectivity assay appropriate for detecting the challenge virus.
Intent-to-treat infected pre-dose (ITT-A) analysis set	All participants having received challenge virus, randomized, and having received at least one dose of IMP, and meeting the criterion for laboratory-confirmed RSV infection (as per ITT-I) while using only assessments prior to taking IMP. The ITT-A analysis set will be considered a secondary analysis population for efficacy endpoints. ITT-A will be a subset of ITT-I.
Intent-to-treat infected post-dose (ITT-B) analysis set	All participants having received challenge virus, randomized, and having received at least one dose of IMP, and meeting the criterion for laboratory-confirmed RSV infection (as per ITT-I) while using only assessments after taking IMP. The ITT-B analysis set will be considered a secondary analysis population for efficacy endpoints. ITT-B will be a subset of ITT-I.
Per protocol (PP) analysis set	All ITT-I analysis set participants who have no major protocol deviations, and who complete the quarantine period up to the final day of quarantine and receive all doses of IMP. Participant exclusions will be determined at a blinded data review meeting (BDRM), which will take place prior to database lock. The PP analysis set will be considered a secondary analysis population for efficacy endpoints.
Safety analysis set	All participants having received challenge virus, regardless of whether they received IMP or not.
Pharmacokinetics (PK) analysis set	All ITT analysis set participants with at least one post-dose PK result. The PK analyses will be performed on the PK analysis set.

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

The study being exploratory by nature, aiming at assessing the true biological effect of the IMP used in the best experimental conditions and not the effectiveness of the strategy to treat participants with the IMP in conditions closest to real life, the primary efficacy analysis will be on the ITT-I analysis set. The ITT-A, ITT-B, and PP analysis sets will be considered a secondary analysis population for efficacy endpoints, as defined in the statistical analysis plan

(SAP). The safety evaluation will be performed on the safety analysis set. Additional analysis sets may be defined in the SAP.

9.4. Statistical Analysis

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

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

9.4.1. Statistical Analysis Plan

Full details of the planned statistical analysis will be presented in the SAP that will provide a more technical, detailed, and comprehensive description of the statistical analyses that will be computed, expanding on the protocol-specified analysis.

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

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

9.4.2. General Considerations

9.4.2.1. Descriptive Statistics

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

Categorical variables will be summarized 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.

9.4.2.2. Inferential Statistics and Significance Testing

Between-group 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 or medians, 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 treatment groups.

9.4.3. Planned Analysis

9.4.3.1. Participant Accountability

The number of participants receiving challenge agent, receiving EDP-323, withdrawing from (also split by reason for withdrawal) and completing the study, and the numbers in each analysis set, will be summarized.

9.4.3.2. Protocol Deviations

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

9.4.3.3. Demographic and Baseline Characteristics

Descriptive statistics of demographics (age, sex, height, body weight, BMI, and ethnicity) will be presented by treatment group 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 treatment group as proportion of participants actually receiving IMP as prescribed.

9.4.4. Primary Efficacy Analysis

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

The main estimator of the primary endpoint, the mean or median VL-AUC of RSV-A Memphis 37b, depending on whether the endpoint is normally distributed, as determined by qRT-PCR on nasal samples (virology) collected twice daily starting 2 days post-viral challenge (Day 2) up to discharge from quarantine, will be analyzed on the ITT-I analysis set.

The calculation of the VL-AUC will be performed on $\log_{10}$-transformed PCR data using the trapezoidal summation rule based on actual time intervals in hours. Results below the lower limit of quantification (LLOQ) will be given values as detailed in the SAP.

Descriptive statistics and the 95% CI will be presented by treatment group. The differences between each active treatment group and the placebo arm will be analyzed using the t-test or Wilcoxon rank sum test, depending on whether the endpoint is normally distributed.

Further details will be described in the SAP.

9.4.5. Secondary Efficacy Analysis

Secondary endpoints as outlined in Section 3, Objectives and Endpoints, will be summarized by treatment group as described in Table 9-2. Further details will be provided in the SAP.

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

Endpoint	Analysis
RSV VLPEAK (RSV viral load by qRT-PCR in nasal samples)	Descriptive statistics for continuous variables (see Section 9.4.2 , General Considerations). Inferential analysis: t-test or Wilcoxon rank sum test.

Endpoint	Analysis
Time to RSV VLPEAK after first dosing (RSV viral load by qRT-PCR in nasal samples)	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). Kaplan Meier estimated will be computed. No inferential analysis.
Time to RSV viral load negativity after first dosing (RSV viral load by qRT-PCR in nasal samples)	
Time to first negative slope of RSV viral load after first dosing (RSV viral load by qRT-PCR in nasal samples)	
Slope of the RSV viral load over time (clearance rate) from time of RSV VLPEAK to 1, 2, 3, and 4 days later (RSV viral load by qRT-PCR in nasal samples)	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). No inferential analysis.
RSV VL-AUC (RSV viral load by cell culture [plaque assay] of nasal samples)	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). Inferential analysis: t-test or Wilcoxon rank sum test.
RSV VLPEAK (RSV viral load by cell culture [plaque assay] of nasal samples)	
Time to RSV VLPEAK after first dosing (RSV viral load by cell culture [plaque assay] of nasal samples)	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). Kaplan Meier estimates will be computed. No inferential analysis.
Time to RSV viral load negativity after first dosing (RSV viral load by cell culture [plaque assay] of nasal samples)	
Time to first negative slope of RSV viral load after first dosing (RSV viral load by cell culture [plaque assay] of nasal samples)	
Slope of the RSV viral load over time (clearance rate) from time of RSV VLPEAK to 1d, 2d, 3d, and 4d later (RSV viral load by cell culture [plaque assay] of nasal samples)	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). No inferential analysis.
TSS-AUC	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). Inferential analysis: t-test or Wilcoxon rank sum test.
Peak TSS	
Time to return to baseline (last assessment before RSV inoculation) TSS	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations). Kaplan Meier estimates will be computed. No inferential analysis.
Time to peak TSS	
Total weight of nasal discharge (mucus) produced	Descriptive statistics for continuous variables (see Section 9.4.2, General Considerations).

Endpoint	Analysis
Total number of tissues used by participants	No inferential analysis

AUC=area under the curve; qRT-PCR=quantitative reverse transcriptase-polymerase chain reaction; RSV=respiratory syncytial virus; TSS=total symptom score; TSS-AUC=area under the total symptom score-time curve; VL-AUC= area under the viral load-time curve; VLPEAK=peak viral load

[redacted]

9.4.7. Safety Analysis

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

Unless otherwise stated in the SAP, 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 (MedDRA) and summarized descriptively by system organ class, preferred term, and treatment group for the number of AEs and the number of TEAEs reported and the number and percentage of participants reporting each AE and TEAE. A TEAE will be defined as any AE that occurs from the time of first study treatment dose administered to the participant until last study visit, i.e. an AE that was not present prior to receiving the first dose of IMP.

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

Other safety endpoints that will be presented by treatment group include laboratory evaluations (biochemistry, hematology, coagulation, 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 EDP-323 (and metabolites) at each applicable time point and for the derived plasma PK parameters. Statistics include sample size (n), mean, standard deviation (SD), CV, geometric mean, median, minimum, and maximum.

For each participant, plasma concentration-time data of EDP-323 (and metabolites) 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.

Plasma PK (AUC) correlations with VL-AUC (e.g., qRT-PCR) and TSS-AUC or other efficacy endpoints may be conducted if supported by the data.

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 analysis is planned for this study.

[redacted]

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 Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

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

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

The PI/investigator will be responsible for the following:

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

10.1.2. Financial Disclosure

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

10.1.3. Confidentiality

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

10.1.4. Informed Consent Process

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

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

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

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

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

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 the study-specific ICF.

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

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 authorized 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 study and sponsor medical monitors which includes safety signal detection at any time during the study.

10.1.7. Dissemination of Clinical Study Data

The key design elements of this protocol will be posted on publicly accessible registry. A 'public registry' is defined as any register on the World Health Organization (WHO) list of primary registries or the International Committee of Medical Journal Editors (ICMJE) list of registries, e.g., ClinicalTrials.gov or International Standardized Randomized Controlled Trial Number (ISRCTN) registry.

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

The PI/investigator shall provide assurance to participants that their confidentiality will be maintained hVIVO have a legal obligation to always protect 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 authorized 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 reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. 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 suggests 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 protocol, the PI/investigator agrees that the results of this study may be used by sponsor in any manner sponsor deems appropriate, including but not limited to regulatory submissions, publications, annual reports and other scientific or business affairs of the company.

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 study, the PI/investigator understands that he/she has an obligation to provide to sponsor complete and accurate results and all data developed during this study.

hVIVO agrees that the first publication of Sponsor Data (as defined in the Master Services Agreement (MSA) shall be made by the sponsor. The sponsor agrees to allow the PI/investigator time to review all manuscripts and abstracts prior to submission for publication, and, that all reasonable comments made by hVIVO in relation to the publication will be considered by sponsor.

If sponsor does not have a publication planned, submitted or under review within twenty-four (24) months after the study has been completed, hVIVO may publish Sponsor Data with sponsor's prior written consent. Subject to terms of the MSA, hVIVO shall be permitted to present at symposia, national or regional professional meetings, and to publish in journals, theses or dissertations, or otherwise of their own choosing, methods and results of the study.

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Prior to submitting or presenting a manuscript or other materials relating to the study to a publisher, reviewer, or other outside person/entity, hVIVO shall provide to sponsor a copy of all such manuscripts and materials, and sponsor shall have at least 60 days from receipt of such manuscripts and material to review and comment. hVIVO agrees that all reasonable comments made by the sponsor in relation to the publication will be considered by hVIVO.

At sponsor's request, hVIVO shall remove any sponsor confidential information, including Sponsor Data, prior to submitting or presenting the materials. Sponsor shall be entitled to require hVIVO to delay any publication for a period of up to 6 months from the date of first submission to the sponsor in order to enable the sponsor to take steps to protect property owned by sponsor and any associated intellectual property rights. hVIVO shall not unreasonably withhold or delay its consent to a request from the sponsor for an exceptional additional delay if, in the reasonable opinion of the sponsor, the property owned by sponsor and any associated intellectual property rights might otherwise be compromised or lost.

For the avoidance of doubt, hVIVO shall not require sponsor's consent nor shall the above requirements apply to any publication of property owned by hVIVO in so far as such publication does not include property owned by sponsor or any other confidential information of 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
Hematology	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) Hemoglobin Hematocrit Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration
Biochemistry	Sodium Potassium Glucose Albumin Chloride Bicarbonate Calcium Uric acid Total protein Creatinine Total, direct, and indirect bilirubin Inorganic phosphate Blood urea nitrogen C-reactive protein Gamma glutamyl transferase Alkaline phosphatase Alanine aminotransferase (ALT) Lactate dehydrogenase Aspartate aminotransferase (AST) Urea

Laboratory Assessments	Parameters
Coagulation	Prothrombin time Activated partial thromboplastin time
Thyroid function	Thyroid stimulating hormone Thyroxine
Cardiac enzymes	Creatine kinase Troponin
Routine urinalysis	Color Specific gravity Appearance pH Presence of blood, glucose, leukocytes, ketones, nitrites, proteins, urobilinogen, and bilirubin by dipstick. If the dipstick yields clinically significant abnormal results: microscopy, culture, and sensitivity examination.
Other screening/eligibility tests	FSH* β-hCG* Urine pregnancy test* Urine drugs of misuse and cotinine Alcohol breath test Total cholesterol** Antibodies against HIV type 1/2 (HIV-1)/(HIV-2) Hepatitis A immunoglobulin M** Hepatitis B surface antigen Hepatitis C antibodies Glycated hemoglobin** Immunoglobulin A antibodies**

* FSH only for postmenopausal 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

Adverse Event 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 unfavorable 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.

Events Meeting the Adverse Event 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 hospitalization. • A clinically significant change in laboratory parameter.

Events NOT Meeting the Adverse Event 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). • Hospitalization 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 SDCs. • 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:

Events NOT Meeting the Adverse Event Definition
○ 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 venipuncture, 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 authorization, in the Summary of Product Characteristics for that product,

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

10.3.4. Serious Adverse Event

Serious Adverse Event 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 hospitalization or prolongation of existing hospitalization**

Serious Adverse Event Definition

- In general, hospitalization 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 hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization 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, diarrhea, 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 jeopardize 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 hospitalization but may jeopardize 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 IB relating to the study in question.

Medical events will be assessed for expectedness against the reference safety information section of the IB or equivalent, and any available IB 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 different from '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
- Severity (or grade)
- 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), stabilization, 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 (SDCs). 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.

Assessment
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 and confirmed by a repeat on the same day) may be judged a grade 1 (mild) AE. However, due to variability in participants' ability to perform these tests with adequate technique, the PI/investigator and/or SME will use his/her clinical judgement to assess whether abnormal spirometry readings are consistent with a true drop and whether an AE should be raised. 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 a spirometry reading on repeat assessment 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 aminotransferase (ALT), aspartate aminotransferase (AST), 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 nonclinically 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 different from '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 Event Severity

Grade	Classification	Definition
Grade 1	Mild	Mild level of discomfort and does not interfere with regular activities.
Grade 2	Moderate	Moderate level of discomfort and significantly interferes with regular activities.
Grade 3	Severe	Significant level of discomfort and prevents regular activities.

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 categorized 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 IB or Product Information (for marketed products) 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 sponsor's medical expert (SME) or the pharmacovigilance representative. However, it is very important that the PI/investigator always assesses causality for every event before the initial transmission of the SAE data to the SME or pharmacovigilance representative.

- 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 categorized as shown in Table 10-3.

Table 10-3: Classification of Adverse Event Relationship

Classification	Definition
Not related	The AE is related to an etiology other than the IMP (the alternative etiology 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 etiology, 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 reduced
- IMP dose increased
- IMP administration interrupted
- IMP administration withdrawn
- Participant withdrawn
- Participant hospitalized
- 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 Event 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.
Not resolved	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
- Stabilized, 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 telephone 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.

All reports should be directed to the SME and pharmacovigilance representative. 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 (SME) or pharmacovigilance representative:	[redacted]
SME SAE telephone number:	Mobile Phone: [redacted]
Pharmacovigilance reporting email:	Email: [redacted]
Pharmacovigilance telephone reporting:	[redacted] Safety Helpline EAPA: [redacted]
SAE email address:	[redacted] Drug Safety Center Email Address EAPA: [redacted]

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 SME and pharmacovigilance representative 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 or pharmacovigilance representative as available, until the SAE has subsided or, in the case of permanent impairment, until it stabilizes, 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 Reactions

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.

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 must be reported by the PI/investigator to the SME 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 IWRS will be used (Section 6.3, Randomization 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 fetal 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, fetal distress, fetal death, stillbirth, congenital anomaly/birth defect, ectopic pregnancy) are considered SAEs.

10.4. Appendix 4: Normal Ranges

hVIVO Normal Ranges for Healthy Participants

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 blood pressure	90	140	mmHg
Diastolic blood pressure	50	90	mmHg

Electrocardiogram

ECG Parameters	Lower Limit	Higher Limit	Units
HR	40	100	Beats per minute
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		Liters
FEV_1/FVC	Normal if ≥70% (≥0.7) of the predicted value		Liters

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.

10.5. Appendix 5: Abbreviations

Abbreviation	Term
AE	Adverse event
ALRI	Acute lower respiratory infection
ALT	Alanine aminotransferase
AM	Alveolar macrophages
AP	Analytical plan
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
AUC	Area under the curve
AUC_{0-24}	Area under the concentration-time curve from time 0 to 24 hours in the dosing period
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 to infinity
AUC_{last}	Area under the concentration-time curve from time 0 to time of last quantifiable concentration
AUC_{0-tau}	Area under the concentration-time curve over the dosing interval
β-hCG	Beta-human chorionic gonadotrophin
BDRM	Blinded data review meeting
BMI	Body mass index
BP	Blood pressure
C_{12h}	Plasma concentration at 12 hours
C_{24h}	Plasma concentration at 24 hours
CI	Confidence interval
CL/F	Apparent systemic clearance (
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DNA	Deoxyribonucleic acid
EC_{90}	90% Effective concentration
ECG	Electrocardiogram
(e)CRF	(Electronic) case report form
FE	Food effect
$FEV_{(1)}$	Forced expiratory volume (in 1 second)
FIH	First-in-human
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GAD	Generalized Anxiety Disorder
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General practitioner
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
IBS	Irritable bowel syndrome
ICF	Inform consent form

Abbreviation	Term
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational medicinal product
ISRCTN	International Standardized Randomized Controlled Trial Number
ITT	Intent-to-treat
ITT-I	Intent-to-treat infected
ITT-A	Intent-to-treat infected pre-dose
ITT-B	Intent-to-treat infected post-dose
IWRS	Interactive web response system
λ_z	Terminal elimination rate constant
LLOQ	Lower limit of quantification
LRT	Lower respiratory tract
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MSA	Master Services Agreement
NGS	Next Generation Sequencing
NOAEL	No observed adverse effect level
PCR	Polymerase chain reaction
PFU	Plaque-forming unit
PHQ	Patient Health Questionnaire
PI	Principal investigator
PK	Pharmacokinetic(s)
PP	Per protocol
QD	Once daily
qicPCR	Qualitative integrative cycler polymerase chain reaction
qRT-PCR	Quantitative reverse transcriptase-polymerase chain reaction
REC	Research Ethics Committee
RiiQ	Respiratory Infection Intensity and Impact Questionnaire
RiiQ-AUC	Area under the total RiiQ-time curve
RNA	Ribonucleic acid
RR	Respiratory rate
RSV	Respiratory syncytial virus
RVAT	Rapid viral antigen test
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SDC	Symptom diary card
SME	Sponsor's medical expert
SoE	Schedule of events
SOP	Standard operating procedure
SpO_2	Peripheral arterial oxygen saturation
SUSAR	Suspected unexpected adverse reaction
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event

Abbreviation	Term
t_{max}	Time to maximum plasma concentration
TSS	Total symptom score
TSS-AUC	Area under the total symptom score-time curve
UK	United Kingdom
URT	Upper respiratory tract
Vd/F	Volume of distribution
VL-AUC	Area under the viral load-time curve
VLPEAK	Peak viral load
WHO	World Health Organization

10.6. Appendix 6: Definitions

10.6.1. General

Term	hVIVO Services Limited Definition
Baseline	For safety assessments the nearest assessments completed prior to inoculation will be used as the baseline measure, unless stated otherwise.
Challenge	The inoculation of a participant with challenge agent inoculum. By definition, the day of challenge is Day 0.
Completion (of a participant's participation in the study)	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.
End-of-study	The end of the study is defined as the date of the last visit of the last participant in the study.
Enrolment (of a participant into the study)	A participant will be considered as enrolled into the study once he/she has been inoculated with the challenge virus. 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	The visit in which the study-specific consent is signed, therefore this may be admission to quarantine.
Infectious titer	The titer of inoculum producing viral infection in a participant. The term 'titer' applies to the quantity or concentration of inoculum (depending on the units documented).
Last study visit	The last visit of the last participant in the study.
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 a human viral challenge study.

Randomization number	The number allocated to a participant at randomization, generated as stated in the protocol (NB. Not applicable will be recorded for "screen fail" participants or participants who are not randomized).
Screen failures	Screen failures are defined as participants who sign the study-specific ICF but are not subsequently enrolled into the study. Screen failures will not be included in the study database. Screen failures may be invited back for repeat assessments and screening and if eligible, for study enrolment.
Subject number	The unique number assigned to a subject in the hVIVO database, which is used to identify a subject prior to randomization. This number will be used throughout the recruitment and generic screening process to identify the subject.

10.6.2. Study Definition of Infection and Illness

Term	**CRITERIA**
Seroconversion	A ≥4-fold increase in RSV-specific antibodies from baseline to follow-up post-quarantine
The following definitions should only be applied to data collected from Day 1 onwards	
Febrile illness	Any occurrence of temperature ≥37.9°C
Laboratory-confirmed RSV infection	• At least 2 positive detections by viral load qRT-PCR assay specific for the challenge virus, reported within 2 consecutive study days and/or • One positive detection by viral load qRT-PCR assay, specific for the challenge virus, in which an aliquot of the same sample has also tested positive in a cell-based infectivity assay appropriate for detecting the challenge virus
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: rhinorrhea (runny nose), nasal congestion (stuffy nose), sore throat, sneezing • Physician findings: nasal discharge, otitis, pharyngitis, sinus tenderness

Term	CRITERIA
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)
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
Viral shedding (for dosing)	One positive detection by qualitative integrative cycler polymerase chain reaction (qicPCR)

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[redacted]

In Person Signer Events	Signature	Timestamp
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	3/27/2024 2:08:44 PM
Certified Delivered	Security Checked	3/27/2024 2:30:18 PM
Signing Complete	Security Checked	3/27/2024 2:30:34 PM
Completed	Security Checked	3/27/2024 2:30:34 PM

Payment Events	Status	Timestamps
Electronic Record and Signature Disclosure		