Protocol Number: EDP 938-101

Official Title: Randomised, Phase 2a, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Pharmacokinetics and Antiviral Activity of Multiple Doses of Orally Administered EDP-938 Against Respiratory Syncytial Virus Infection in the Virus Challenge Model

NCT Number: NCT03691623

Document Date: 07 NOV 2019

CLINICAL STUDY PROTOCOL

[redacted]

Sponsor's study number: EDP 938-101

hVIVO Protocol No: ENA-CS-001

A Randomised, Phase 2a, Double-Blind, Placebo-Controlled study to Evaluate the Safety, Pharmacokinetics and Antiviral Activity of Multiple Doses of Orally Administered EDP-938 Against Respiratory Syncytial Virus Infection in the Virus Challenge Model.

Short title:	Safety, Pharmacokinetics and Antiviral Activity of Orally Administered EDP-938 Against RSV
Version:	Amendment 4.0 (version 5.0) Date 07NOV2019
Sponsor:	ENANTA Pharmaceuticals, Inc 500 Arsenal Street Watertown, MA 02472 United States of America (USA).
Principal Investigator:	[redacted] hVIVO Services Limited (hVIVO), Queen Mary BioEnterprises Innovation Centre, 42 New Road, London E1 2AX, United Kingdom (UK).
Study carried out at the facilities of:	hVIVO Services Limited, Queen Mary BioEnterprises Innovation Centre, 42 New Road, London. E1 2AX. United Kingdom.
EUDRACT Number:	2018-001878-21

Are any sub-studies in progress at the trial sites? **Yes** ☐ **No** ☒

PROTOCOL AMENDMENT

Protocol Number	Date	Type	Brief details
1.0	23JULY2018	Original Protocol	N/A
Amendment 1.0 (v2.0)	04SEP2018	[redacted]	Section 7.3: Inclusion criteria #4 updated to reduce BMI upper limit of 30kg/m^2 Section 7.3: Inclusion criteria #5 on contraception updated to align with contraceptive methods in the Clinical Trials Facilitation Group (GTFG) guidance. Section 18.5.1: Stopping criteria for the study updated to provide definitive stopping criteria information and Table 18.1
		Clarification of PK Blood sampling for Dose 9 and Dose 10	Section 21: Appendix 7 - PK Blood Sampling Schedule clarified for Dose 9, 12-hours post dose sample, and dose 10 pre-dose.
		Administrative correction	Section 3: Glossary of Abbreviations: SME abbreviation clarified
Amendment 2.0 (v3.0)	30OCT2018	[redacted]	[redacted]
		Clarification of the 72h PK plasma sample collection post last dose for Part 1	Table 9-1 (Time and events schedule) footnote updated to clarify the 72h PK plasma sample collection for subjects who started dosing on the

			afternoon of Day 5 post viral challenge. Appendix 7 footnote added to clarify the 72h PK plasma sample collection post last dose for Part 1.
		Clarification of rescreening process	Section 9.3.1 clarified rescreening process for subjects who are found ineligible based on review of eligibility criteria.
Amendment 3.0 (v4.0)	11JUL2019	[redacted]	[redacted]
		Confirmation of the treatment groups for Part 2	Section 9.1 updated to include a confirmation of the treatment groups for Part 2 following the emerging data from Part 1. Due to the combination in dosing schedule (i.e OD and BD) all subjects will be treated Twice daily (similar to part 1) in order to maintain the blind between treatment groups. The duration of dosing for Part 2 clarified as a 5 days dosing regimen. The number of subjects enrolled in each of the treatment groups for Part 2 confirmed as n=21 subjects per treatment group.
		Clarification of the randomisation ratio for Part 2	Section 10.1: randomisation ratio for Part 2 clarified as a 1:1:1 ratio.

		Clarification of the PK blood sampling schedule for Part 2	Appendix 7: PK blood sampling schedule for Part 2 clarified.
		Clarification of adverse events reporting for 15% drop in spirometry value	Section 15 Adverse Events and Toxicity Management clarified for the reporting of adverse events related to a 15% drop in spirometry value.
Amendment 4.0 (v5.0)	07NOV2019	[redacted]	[redacted]

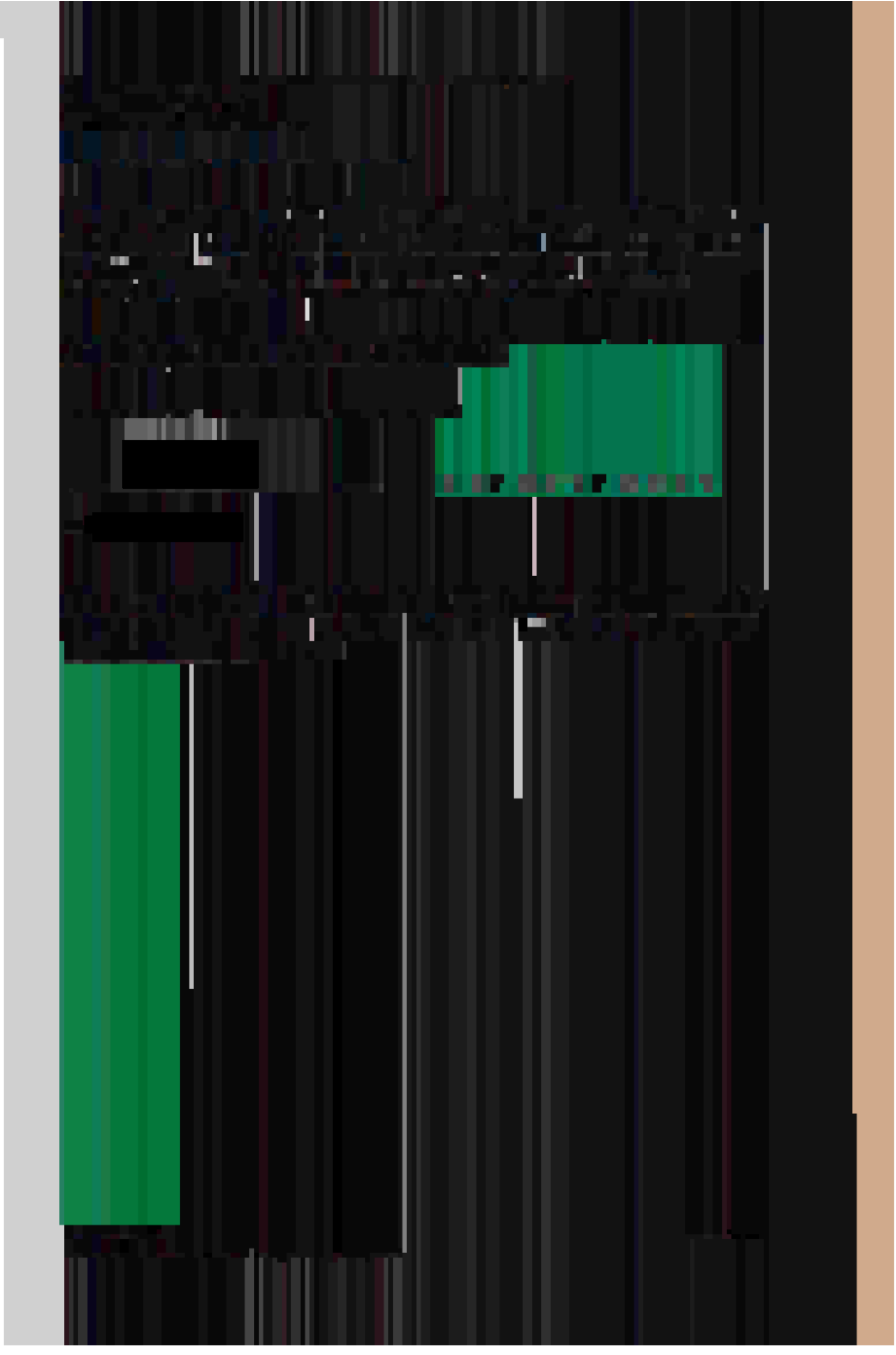
SPONSOR'S AUTHORISATION

This clinical trial protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product (IMP), and with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki 2013[1] and the principles of the International Conference on the Harmonisation of Good Clinical Practice (ICH GCP)[2] as applicable to this clinical trial.

The Sponsor will provide an Investigator's Brochure (IB) and/or an Investigational Medicinal Product Dossier (IMPD), giving information about the chemistry, manufacture and controls, and the pharmacological and toxicological properties of the IMP, and summarising any clinical experience of the compound. Additional information regarding the IMP will be provided to the Principal Investigator (PI) when it becomes available. The Sponsor will also provide appropriate documentation relating to the clinical trial supplies, including certificates of analyses and confirmation of current Good Manufacturing Practice (GMP)[3] compliance in their manufacture.

A designated professional representative of the Sponsor will conduct visits to the investigational site(s) at appropriate intervals throughout the study, in order to verify adherence to the protocol and the accurate and complete recording of data in the source documents and drug inventory forms.

SIGNATURE OF THE SPONSOR'S REPRESENTATIVE
SIGN [redacted] _____ DATE / /
NAME [redacted]



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1 STUDY PERSONNEL CONTACT LIST

CONTACT	DETAILS
SPONSOR	ENANTA Pharmaceuticals Inc 500 Arsenal Street Watertown, MA 02472 United States of America (USA).
PRINCIPAL INVESTIGATOR (PI) AND TRIAL SITE	[redacted] hVIVO Services Limited (hVIVO), Queen Mary BioEnterprises Innovation Centre, 42 New Road, London E1 2AX United Kingdom (UK). [redacted]
SPONSOR'S REPRESENTATIVE	[redacted] Sr. Director, Head of Clinical Operations ENANTA Pharmaceuticals, Inc. 500 Arsenal Street Watertown, MA 02472 [redacted]
SPONSOR'S MEDICAL MONITOR	[redacted] SVP, Chief Medical Officer Enanta Pharmaceuticals, Inc. 500 Arsenal Street Watertown, MA 02472 [redacted]
PHARMACOVIGILANCE VENDOR	[redacted]
GMP MANUFACTURER	Hammersmith Medicines Research Pharmacy Department Cumberland Avenue. London NW10 7EW. United Kingdom (UK) Phone: +44 (0) 20 8963 4508 / +44 (0) 800 783 8792 Fax: +44 (0) 20 8961 3130
BIOANALYTICAL LABORATORY	hVIVO Services Limited (hVIVO), Queen Mary BioEnterprises Innovation Centre, 42 New Road, London E1 2AX United Kingdom (UK)

OTHER PARTIES	The Sponsor Trial Master File (TMF) / hVIVO TMF contains details of third party contractors, sub-investigators, laboratories, clinical monitors, data management suppliers, statisticians and all other service providers.

2 PROTOCOL SYNOPSIS

SYNOPSIS	
SPONSOR PROTOCOL NO.	EDP 938-101
EUDRACT NUMBER	2018-001878-21
hVIVO PROTOCOL NUMBER	ENA-CS-001
TITLE	A Randomised, Phase 2a, Double-Blind, Placebo-Controlled study to Evaluate the Safety, Pharmacokinetics and Antiviral Activity of Multiple Doses of Orally Administered EDP-938 Against Respiratory Syncytial Virus Infection in the Virus Challenge Model.
SPONSOR	ENANTA Pharmaceuticals Inc.
DESIGN	A randomised, Phase 2a, double-blind, placebo-controlled, two-part study to evaluate the safety, pharmacokinetics and antiviral activity of multiple doses of orally administered EDP-938 in healthy subjects infected with RSV-A Memphis 37b.
PHASE	2a
CHALLENGE VIRUS	RSV-A Memphis 37b
CHALLENGE VIRUS ROUTE	Intranasal (both nostrils)
CHALLENGE VIRUS TITRE	Each subject will receive ~ 4 Log10 PFU
INDICATION	Respiratory Syncytial Virus (RSV) infection
IMP	EDP-938 [redacted] or Placebo
IMP DOSE(S)	Part 1: • 114 subjects will be randomised into 1 of 3 treatment groups for 5 days of dosing: o Group 1: Placebo (n=38); subjects in this group will receive placebo dose TWICE a day (BD) (every 12 hours (±1 hour) interval) for a total of 10 doses. o Group 2: EDP-938 oral [redacted] loading dose group (n=38): subjects in this group will receive a single Loading Dose (LD) of 500mg followed by 300mg dose BD. This group will receive 500mg first dose, and at 12 hours (±1 hour) interval receive 300mg second dose, then 300mg doses BD for a total of 10 doses. o Group 3: EDP-938 oral [redacted] 600mg dose group (n=38): subjects in this group will receive a daily 600mg dose followed by a placebo dose at 12 hours (±1 hour) interval for a total of 10 doses.

SYNOPSIS	
	Part 2: • Up to a maximum of 84 subjects in total for Part 2 will be enrolled following an analysis of Part 1. Up to 63 subjects will complete dosing with EDP-938 and up to 21 subjects will complete dosing with placebo. • The dose(s) of EDP-938 selected will be projected to deliver an efficacious exposure and will be based on emerging PK, PK/PD modelling, virology, clinical symptom score, and safety data. • However, the maximum individual dose in any treatment regimen will not exceed a loading dose followed by maintenance doses which are projected to deliver mean IMP exposure of 28745 ng.hr/mL (AUC) • In Part 2, 63 subjects will be randomised equally into 1 of 3 treatment groups as below. Additional treatment groups may be evaluated, however, the maximum number of subjects enrolled in Part 2 will be 84. o Group 1 (n=21): Placebo dosed TWICE daily (BD) for 5 days, with dosing at 12 hours (± 1 hour) interval, o Group 2 (n=21): A single Loading Dose of 400mg (Dose 1) followed by 200mg second dose at 12 hours (± 1-hour interval), then 200mg doses BD, and with dosing for 5 days, o Group 3 (n=21): A single Loading Dose of 600mg (Dose 1), followed by a 300mg dose ONCE a day (OD) (every 24 hours (±1 hour) interval) dosing , and with dosing for 5 days. • In order to maintain the study blind, subjects in the active OD dosing group will have their regimen supplemented by the administration of a placebo matched to EDP-938 in order to mimic the BD dosing group.
PHARMACEUTICAL FORM	[redacted] EDP-938 [redacted]
IMP ROUTE(S)	Oral [redacted]
CONTROL COMPOUND	Placebo [redacted]
[redacted]	[redacted]

SYNOPSIS	
	The administration of a placebo matched to EDP-938 will ensure treatment blinding is maintained.
STUDY POPULATION	Healthy Subjects
SAMPLE SIZE	Up to 198 subjects
REPLACEMENT POLICY	Subjects that have been inoculated but not dosed will be replaced. Subjects who are withdrawn before they have received all doses of IMP (i.e. subject has received at least one IMP dose) will not be replaced. If any of the quarantine groups has less than the planned number of subjects, additional subjects may be recruited into later quarantines, or additional quarantines may be conducted in order to maintain the power of the study.
PRIMARY OBJECTIVE	To evaluate the antiviral activity of EDP-938 compared to placebo in healthy adult subjects inoculated with RSV-A Memphis 37b.
PRIMARY ENDPOINT	The area under the curve (AUC) for RSV viral load measured in nasal washes by quantitative reverse transcription polymerase chain reaction (RT-qPCR), in subjects inoculated with RSV-A Memphis 37b.
SECONDARY OBJECTIVES	To evaluate EDP-938 compared to placebo in healthy adult subjects inoculated with RSV-A Memphis 37b in terms of: o Clinical symptoms o Viral load o Safety and Tolerability To characterise the PK profile of multiple doses of EDP-938 and metabolites in healthy adult subjects inoculated with RSV-A Memphis 37b. To characterise the relationship between Plasma PK of EDP-938 and viral load AUC (RT-PCR) and total symptom score AUC.
SECONDARY ENDPOINTS	Secondary endpoints relating to efficacy include, but not limited to: Clinical Symptoms: o Effect of EDP-938 compared to placebo on RSV symptoms (using the 10- item diary card), with endpoints including: ▪ AUC of total symptom score ▪ Peak total symptom score over the duration of quarantine

SYNOPSIS	
	▪ Total symptom score ▪ Time to peak symptom score after IMP dosing. ▪ Time to resolution from peak symptom. o Total weight of nasal mucus produced (via weighed paper tissues). Viral Load: o Additional viral load endpoints calculated separately using data from RT-qPCR of nasal wash comparing placebo and EDP-938 treated including: ▪ Peak viral load ▪ Time to peak viral load ▪ Time to resolution from peak ▪ Time to cessation of virus quantifiable post first dosing Secondary endpoints relating to safety include, but are not limited to: • Adverse Events (AEs) • Physical Examination • Vital signs • 12-lead Electrocardiograms (ECGs) • Spirometry • Clinical laboratory results (including biochemistry, haematology, coagulation (if required), cardiac enzymes and urine analysis) Secondary endpoints related to PK include, but are not limited to: • Plasma PK parameters of EDP938 (and metabolites) following repeat dose administration in healthy adult subjects inoculated with RSV-A Memphis 37b: C_{max}, T_{max}, $t_{1/2}$, CL/F, λ_z, Vd/F, C12, C24, AUC_{last}, $AUC_{0\text{-}tau}$, or $AUC_{0\text{-}inf}$ • Plasma PK (AUC) correlations with viral load AUC (e.g. RT-PCR) and TSS AUC
[redacted]	[redacted]

SYNOPSIS	
[redacted]	[redacted]
[redacted]	[redacted]
SUMMARY OF STUDY DESIGN	• Screening Visit from Day -56 to Day -3 Historical pre-screening data collected through the hVIVO generic screening process within 56 days to 3 days prior to inoculation (90 days for viral serology) may be used for screening procedures. Historical pre-screening data obtained prior to this window can be re-assessed any time within 56 days to 3 days prior to Inoculation. • Entry to quarantine on Day -2 or Day -1 • Challenge Virus inoculation on Day 0 • In Part 1: 5 consecutive days of dosing: o Group 1: Placebo (n=38): subjects in this group will receive placebo dose TWICE a day (BD) (every 12 hours (±1 hour) interval) for a total of 10 doses.

SYNOPSIS	
	○ Group 2: EDP-938 oral suspension loading dose group (n=38); subjects in this group will receive 500mg first dose, and at 12 hours (±1 hour) interval) receive 300mg second dose, then 300mg doses BD for a total of 10 doses. ○ Group 3: EDP-938 oral suspension 600mg dose group (n=38): subjects in this group will receive a daily 600mg dose, followed by a placebo dose at 12 hours (±1 hour) interval for a total of 10 doses. • IMP dosing to start on confirmation of positive result by qualitative integrated cycler polymerase chain reaction (qicPCR) on nasal wash. Nasal wash for qicPCR will be performed twice daily (BD) on Study Days 2-5 (Study Day 5 morning only), or until a positive result is achieved, whichever is sooner. • IMP dosing will be initiated 12 hours (± 1hour) post nasal wash confirmation of a positive qicPCR result. • Earliest start of IMP dosing will be in the evening on Study Day 2 post viral challenge. **OR** • Dosing will start in the evening of Study Day 5 if no positive result is obtained by qicPCR. An analysis of the available safety, PK, virology, and clinical symptom score data will be conducted at the end of the Part 1. • In Part 2: • Up to a maximum of 84 subjects in total for Part 2 will be enrolled following an analysis of Part 1. Up to 63 subjects will complete dosing with EDP-938 and up to 21 subjects will complete dosing with placebo. The dose(s) of EDP-938 selected will be projected to deliver an efficacious exposure and will be based on safety, PK, PK/PD modelling, virology, and clinical symptom score data. However, the maximum individual dose in any treatment regimen will not exceed a loading dose followed by maintenance doses which are projected to deliver mean IMP exposure of 28745 ng.hr/mL (AUC) • In Part 2, 63 subjects will be randomised equally into 1 of 3 treatment groups as below. Additional treatment groups may be evaluated, however, the maximum number of subjects enrolled in Part 2 will be 84.

SYNOPSIS	
	○ Group 1 (n=21): Placebo dosed TWICE daily (BD) for 5 days, with dosing at 12 hours (± 1 hour) interval, ○ Group 2 (n=21): A single Loading Dose of 400mg (Dose 1), followed by 200mg second dose at 12 hours (± 1-hour interval), then 200mg doses BD, and with dosing for 5 days, ○ Group 3 (n=21): A single Loading Dose of 600mg (Dose 1), followed by a 300mg dose ONCE a day (OD) (every 24 hours (±1 hour) interval) dosing, and with dosing for 5 days. • In order to maintain the study blind, subjects in the active OD dosing group will have their regimen supplemented by the administration of a placebo matched to EDP-938 in order to mimic the BD dosing group. **Part 2 Progression and Additional Evaluation Guidelines:** Part 2 will commence no earlier than after an evaluation by the Sponsor and Investigator of the virology, clinical symptom score, PK, and safety data from Part 1. Prior to Part 2 the Sponsor will review the emerging data to confirm dose(s) (up to 600mg dose) and dose frequencies (OD or BD) to be evaluated in Part 2. Higher doses may be evaluated in the event that there is the potential for additional antiviral responses; PK exposures are projected to remain within the limits to deliver mean IMP exposure of 28745 ng.hr/mL (AUC); and an acceptable safety profile is observed. Lower doses may be evaluated in the event that a degree of viral suppression is observed. A longer duration of dosing (up to 7 days maximum) may be evaluated if there is evidence of incomplete viral suppression or viral rebound after completion of therapy, and an acceptable safety profile is observed. See section 18.5.1 for stopping criteria. The maximum dose administered in any part of this study will not exceed PK exposures projected deliver mean IMP exposure of 28745 ng.hr/mL (AUC). The maximum duration of treatment in parts 1 & 2 will not exceed 5 days and 7 days respectively. • Subjects will be resident in the Quarantine Unit for a total of approximately 15 days (from Day -2/-1 to Day 12)

SYNOPSIS	
	• End of quarantine phase on Day 12 (or longer based on the subject's clinical condition or/and at the PI's discretion) • Follow-up Visit(s): Part 1: • (Study Day 28 [± 3 days]) and study termination Part 2: • Study Day 13, where applicable (only subjects who started IMP dosing on the evening of Study Day 5 (up to Day 8 evening) will return for a PK sample on Study Day 13) • Study Day 14, where applicable (only subjects who started IMP dosing on the evening of Study Day 5 (up to Day 8 evening) will return for a PK sample on Study Day 14) • Study Day 15, where applicable (only subjects who started IMP dosing on the evening of Study Day 5 (up to Day 8 evening) will return for a PK sample on Study Day 15) • Study Day 16, where applicable (only subjects who started IMP dosing on the evening of Study Day 5 (up to Day 8 evening) will return for a PK sample on Study Day 16) • Study Day 17, where applicable (only subjects who started IMP dosing on the evening of Study Day 5 (up to Day 8 evening) will return for a PK sample on Study Day 17) • Study Day 18, where applicable (only subjects who started IMP dosing on the evening of Study Day 5 (up to Day 8 evening) will return for a PK sample on Study Day 18) • Study Day 28 [± 3 days] and study termination
PROCEDURES AND ASSESSMENTS	During the study the following assessments and procedures will be performed: • Written informed consent • Eligibility criteria • Height, body weight, body mass index (BMI) • Medical history • Demographics • Prior medications • Challenge Virus inoculation • Randomisation • Dosing with IMP (study drug/placebo)

SYNOPSIS	

	• Complete physical examination
	• Directed physical examination (including nasal examination)
	• Vital signs (blood pressure [BP], respiratory rate [RR], heart rate [HR], saturation of peripheral oxygen [SpO_2])
	• Tympanic Temperature [TT]
	• 12-lead ECG
	• Spirometry
	• 24-hour tissue count and mucus weight
	• Symptom diary card
	• Bloods:
	  ○ RSV serology
	  ○ haematology
	  ○ biochemistry
	  ○ coagulation
	  ○ cardiac enzymes
	  ○ thyroid function test (TFT)
	  ○ hepatitis A, B and C and human immunodeficiency virus (HIV) serology
	  ○ serum follicle stimulating hormone (FSH) (Post-menopausal females only)
	  ○ beta-human chorionic gonadotropin (β-hCG) pregnancy test (females only)
	• Nasal discharge collection
	  ○ 24-hour nasal discharge weight.
	  ○ Number of paper tissue used for nasal discharge over 24-hour period
	• Pharmacokinetic (PK) samples
	  ○ plasma
	• Nasopharyngeal swab
	  ○ respiratory virus screen
	  ○ rapid viral antigen test (RVAT)
	• Nasal wash
	  ○ qicPCR
	  ○ RSV-A Memphis 37b viral load (RT-qPCR)
	  ○ cell based infectivity assay e.g. plaque assay
	  ○ resistance monitoring
	  ○ replicative strand PCR (cells)
	  ○ PK samples
	• Breath alcohol test
	• Urine
	  ○ urinalysis (dipstick test)
	  ○ pregnancy test
	  ○ drugs of abuse and cotinine screen
	• AEs/Concomitant medications
	• Patient Health Questionnaire (PHQ-9) at the Investigator's discretion
	• Generalised Anxiety Disorder Questionnaire (GAD-7), at the Investigator's discretion

SYNOPSIS	
END OF STUDY	The last subject's last scheduled visit (LSLV).
EXPECTED DURATION OF SUBJECT PARTICIPATION	A maximum of approximately 3 months, from screening at Day -56 to the last scheduled visit at Day 28.
OVERALL DURATION OF CLINICAL PHASE	Approximately 18 months (first subject screened to LSLV) including Part 1 and Part 2.
STATISTICS	The sample size was calculated based on the assumption of a 70% reduction (i.e. difference of 21.3 Log_{10} PFUe/mL * days) in (RT-qPCR) viral load AUC with a within-group standard deviation of 16.9 Log_{10} PFUe/mL*days (i.e. 56% Coefficient of Variation (CV)) (based on similar previous study), power of 80% and a two-sided 5% level of significance. On this basis, it is estimated that 12 evaluable RSV-A Memphis 37b infected (ITT-I) subjects per treatment group would be sufficient for the study. However, with the assumption of a 56% infection rate and dropouts during the post-inoculation period, 22 recruited subjects would be required for sufficient power to assess the CA endpoint. Considering the secondary endpoint of Total Symptom Score (TSS) AUC, a 70% reduction in TSS AUC with an assumed CV of 79% would require 21 evaluable (ITT-I) subjects per treatment group. Taking into account dropouts and infection rate this would require 38 recruited subjects per treatment group (114 in total for two active treatment groups and one placebo group) for Part 1. Primary and secondary endpoints will be summarised using descriptive statistics. Continuous variables will be summarised using number of observations, mean (and/or geometric mean, where applicable), standard deviation, standard error, median, lower quartile, upper quartile, minimum and maximum values. Categorical variables will be summarised using proportions (counts and percentages). Statistical analyses will be performed using appropriate two-sided hypothesis tests at the 5% significance level. Normally distributed continuous variables will be presented as mean, difference in means and a 95% confidence interval (CI). The t-test will be used to compare means between groups (or an appropriate alternative test, if the t-test assumptions are not satisfied). For endpoints that are not normally distributed (such as total symptom scores), the Wilcoxon Rank-Sum test will be used. Any missing data will be accounted for, and their possible impact on the study analysis will be described within the Statistical Analysis Plan (SAP).

3 GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
ABPI	Association of British Pharmaceutical Industries
ADR	Adverse Drug Reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Analytical Plan
APTT	Activated partial thromboplastin time
AR	Adverse reaction
ASR	Annual Safety Report
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under (the) curve
BCRP	Breast Cancer Resistance Protein
BD	Twice daily
BID	Twice daily
BDRM	Blinded data review meeting
β-hCG	Beta human chorionic gonadotropin
BMI	Body mass index
BP	Blood Pressure
bpm	Beats per minute
CFR	Code of Federal Regulations
CK	Creatine kinase
COPD	Chronic obstructive pulmonary disease
C_{max}	Maximum (peak) observed concentration
CRA	Clinical Research Associate
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical study report
CYP450	Cytochrome P 450
CTA	Clinical Trial Agreement
CV	Coefficient of Variation
DFA	Direct fluorescent antibody assay
DMP	Data Management Plan
DSUR	Development Safety Update Report
DTA	Data Transfer Agreement
ECG	Electrocardiogram
eCRF	Electronic case report form
ECCS	European Community for Coal and Steel
ERS	European Respiratory Society
EU	European Union
FE	Food Effect
FEV_1	Forced expiratory volume in 1 second
FI	Febrile illness
FIH	First-In-Human
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GAD-7	Generalised Anxiety Disorder-7 (Questionnaire)
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HAV	Hepatitis A Virus
HBEC	Human Bronchial Epithelial Cells
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus

Abbreviation	Term
HDPE	High-Density Polyethylene
HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
HMR	Hammersmith Medicines Research
HR	Heart rate
HVC	Human Viral Challenge
hVIVO	hVIVO Services Limited
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICF	Informed consent form
IMP	Investigational medicinal product
IMPD	Investigational Medicinal Product Dossier
ITT	Intention-to-treat
ITT-I	Intention-to-treat- Infected
IUD	Intra uterine device
IUS	Intra uterine system
IV	Intravenous
LD	Loading Dose
LRT	Lower respiratory tract
LRTI	Lower respiratory tract illness
LSLV	Last subject last (scheduled) visit
MAD	Multiple Ascending Dose
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCS	Microscopy, sensitivity and culture
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
mm Hg	Millimetres of mercury
MRSD	Maximum Recommended Starting Dose
N	Nucleoprotein
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NTF	Note to file
OD	Once daily
OTC	Over-the-counter
PCR	Polymerase chain reaction
PFU	Plaque Forming Unit (for RSV)
P-gp	P-glycoprotein
Ph. Eur	European Pharmacopoeia
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PK	Pharmacokinetics
PO	Oral
PP	Per protocol
PT	Prothrombin time
QA	Quality assurance
QC	Quality control
QP	Qualified Person
qPCR	Quantitative polymerase chain reaction
qicPCR	Qualitative integrated cycler polymerase chain reaction
REC	Research Ethics Committee
RR	Respiration Rate
RSI	Reference Safety Information
RSV	Respiratory Syncytial Virus
RT-qPCR	Quantitative Reverse Transcription Polymerase Chain Reaction
RVAT	Rapid virus antigen test
SAD	Single Ascending Dose
SAE	Serious adverse event

Abbreviation	Term
SAP	Statistical Analysis Plan
SAR	Serious adverse drug reaction
SD	Standard deviation
SDMP	Source Data Management Plan
SI	Systemic illness/Statutory Instrument
SMM	Sponsor's Medical Monitor
SME	Sponsor's Medical Expert
SOP	Standard operating procedure
SpO_2	Saturation of peripheral oxygen
ssRNA	single-stranded ribonucleic acid
SUSAR	Suspected unexpected serious adverse reaction
TDS	Three times daily
TFT	Thyroid function test
T_{max}	Observed timepoint of C_{max}
TMF	Trial Master File
TSH	Thyroid stimulating hormone
TT	Tympanic temperature
UK	United Kingdom
URT	Upper respiratory tract
URTI	Upper respiratory tract illness
US/USA	United States of America
USM	Urgent safety measures
USP	United States Pharmacopeia
VIS	Subject information sheet
WBC	White blood cell
WHO	World Health Organization

4 DEFINITIONS

4.1 General

TERM	Definition
Completion (of a subject's participation in the study)	A subject will be considered to have completed the study after his/her attendance at the last scheduled study visit Day 28 (±3 days), or the last unscheduled visit as applicable.
Baseline (for statistical analysis)	The nearest assessments completed prior to inoculation (for safety assessments) or prior to dosing (for efficacy assessments) will be used as the baseline measure, unless stated otherwise.
Enrolment (of a subject into the study)	A subject will be considered to be `enrolled` into the study once he/she has been randomised, dosed, or inoculated (whichever occurs first).
Infectious titre	The titre of virus inoculum producing viral infection in a subject. The term 'titre' applies to the quantity or concentration of virus inoculum (depending on the units documented).
Quarantine group	A group of subjects who are admitted to and are resident in the Quarantine Unit for a particular quarantine period (i.e., subjects whose Day 0 and scheduled discharge date are the same).
Quarantine period	The period of time when clinical trial subjects are isolated in the Quarantine Unit during a HVC study.
Randomisation	A method based on chance alone by which subjects are assigned to a treatment group.
Randomisation number	The number allocated to a subject at randomisation.
Study day	'Study Day' relates to the day in relation to Viral Challenge: ▪ The day of Viral Challenge is referred to as Study Day 0. ▪ Study days prior to the day of Viral Challenge are for example 'Study Day -2', 'Study Day -1'. ▪ Study days after Viral Challenge are 'Study Day 1', 'Study Day 2' etc. to 'Study Day 28' (final scheduled follow-up).
Subject number	The unique number assigned to a subject on the hVIVO subject database, which is used to identify the subject prior to randomisation.
Treatment cohort	The group of subjects who are receiving the same treatment regimen (i.e. subjects who are receiving the same IMP schedule (dosage, duration, etc.).

TERM	Definition
Viral Challenge (or Challenge)	The inoculation of a subject with virus inoculum. By definition, the day of Viral Challenge is Day 0.

4.2 Study definitions of infection and illness

TERM	CRITERIA
The following definitions should only be applied to data collected from Day 1 onwards	
Lower Respiratory Tract Illness (LRTI)	Any one of the following signs and/or symptoms on two consecutive scheduled assessments, at least one of which must feature Grade 2 severity, or if any of the following attain Grade 3 severity once: o Self-reported symptoms: cough, shortness of breath o Physician findings: wheezes, rhonchi
Upper Respiratory Tract Illness (URTI)	Any one of the following signs and/or symptoms on two consecutive scheduled assessments, at least one of which must feature Grade 2 severity, or if any of the following attain Grade 3 severity once: o Self-reported symptoms: rhinorrhoea (runny nose), nasal congestion (stuffy nose), sore throat, sneezing, earache. o Physician findings: nasal discharge, otitis, pharyngitis, sinus tenderness.
Systemic Illness	Fulfils the criteria for febrile illness, or fulfils the definition of upper respiratory tract illness and/or lower respiratory tract illness **And** Any one of the following symptoms on two 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 • [redacted]

TERM	CRITERIA
Febrile Illness	Any occurrence of temperature ≥ 37.9 ºC (confirmed by a repeat measurement as ≥ 37.9 ºC within 20 to 60 minutes), **OR** Temperature change (post inoculation) of ≥ 2 standard deviations (SD) greater than a baseline measure (from all scheduled temperatures taken by any method on Days -2, -1 and Pre-challenge on Day 0).
Viral shedding	**One or both** of the following definitions must be met: • At least 2 positive quantifiable detections by viral load qPCR assay specific for the challenge virus, reported on 2 or more consecutive days; • One positive detection by viral load RT-qPCR assay, specific for the challenge virus, in which an aliquot of the same sample has also tested positive in a cell based assay appropriate for detecting the challenge virus.
Laboratory confirmed RSV infection	Viral shedding definition has been met.

5 BACKGROUND AND INTRODUCTION

5.1 Information about Respiratory Syncytial Virus (RSV)

RSV Virus Challenge strain Memphis-37b strain has been utilised in over 900 healthy subjects in at least 17 clinical studies. RSV inoculation of healthy subjects was shown to infect approximately 65 - 85% of placebo subjects and produced mild to moderate upper respiratory tract illness[24].

Additionally, another sub-batch of live RSV (Memphis 37c) has been used as a challenge agent and was shown to be safe in over 77 healthy young adults across three studies. RSV infection was not associated with any serious adverse side effects[7-9].

The study virus, like many viruses, can cause more substantial health issues such as myocarditis (inflammation or damage to the heart muscle). However, the chance of this resulting in serious or permanent changes is rare, as most cases are minor and resolve without any lasting changes. In our virus challenge studies, uncommonly blood tests have shown a change suggestive of myocarditis, although in these few subjects the blood tests returned to normal without treatment and were not associated with specific symptoms or ECG changes.

Human RSV is an enveloped, single-stranded ribonucleic acid (ssRNA) virus, which infects all human age groups, but causes the most severe disease burden in the paediatric population. RSV infects over half of all infants within their first year of life[10], and is the single most common cause of hospitalisation of infants[11, 12], representing more than 126,000 childhood hospitalisations per year in the United States (US) and a similar number in the European Union (EU)[13]. Furthermore, the development of childhood asthma and other post-acute sequelae is also known to occur after severe childhood RSV infections[14-16].
Childhood infection is not associated with life-long immunity to RSV and infections in adulthood occur periodically with an acute, mild rhinitis[10, 14, 17]. In susceptible adult populations (e.g., the elderly, those with co-existing heart or lung disease, individuals receiving chemotherapy or who are immuno-compromised), RSV can produce more severe and potentially life-threatening lower respiratory tract infections[18-22].
No vaccine to treat or prevent RSV mediated disease is available. The only approved antiviral therapy for RSV, ribavirin, is rarely used in the US or European paediatric population due to its unfavourable toxicity, its poor antiviral effect, and its controversial and limited efficacy[23-25].
Existing prevention strategies rely on monoclonal antibodies which are only partially effective and which are administered to only a small fraction of the at-risk population[26]. Thus, an effective therapy for RSV infection represents a major unmet medical need.

5.2 Information about EDP-938

5.2.1 Product description

The study drug is EDP-938, is a novel, orally administered, non-fusion replication inhibitor of RSV that is being developed as a potential treatment for RSV infection.

EDP-938 is a small molecule, with a molecular formula $C_{27}H_{22}F_3N_7O_3$. The drug product is [redacted]

5.2.2 Non-clinical studies

5.2.2.1 Non-Clinical Pharmacology Studies

The principal findings from the non-clinical pharmacology studies are summarised below:

- EDP-938 is a novel non-fusion replication inhibitor of RSV with *in vitro* resistance studies suggesting that the compound targets RSV nucleoprotein (N)[48-49].
- It is specific for RSV with no cross-activity against two unrelated viruses, HBV and HCV, and the antiviral effect is not due to cytotoxicity.
- *In vitro* resistance study revealed that mutations selected with EDP-938 are mainly located in the P-binding pocket of RSV N protein, which is consistent with previous reports with other inhibitors of the same class[48].
- RSV N protein is an essential component of viral RNA-dependent RNA polymerase (RdRp), which is responsible for viral replication and transcription. *In vitro* time-of-addition study confirms that EDP-938 works at a post-entry, replication step of RSV.
- [redacted]
- Taken together, these data suggest that the anti-RSV effect of EDP-938 is likely mediated through viral N protein, although the exact mechanism of action remains to be further elucidated.

5.2.2.2 Non-Clinical Pharmacokinetics

The PK properties of EDP-938 were investigated in non-clinical studies conducted [redacted] The PK of EDP-938 following single intravenous (IV) and oral (PO) doses were determined in each of these animal species. In addition, multiple-dose oral pharmacokinetic studies were conducted as components [redacted] Good Laboratory Practice (GLP) toxicology studies in mice and monkeys. The mouse and the monkey comprised the primary species used to evaluate the safety of the compound.

- [redacted]
- [redacted]

- [redacted]

- [redacted]

- [redacted]

5.2.2.3 Non-Clinical Toxicology in Animal Summary

Key findings from these studies are summarised below:

- Oral EDP-938 treatment in single and repeat dose general toxicity studies at up to [redacted] of once-daily dosing across species was well-tolerated.

- [redacted]

- [redacted]

- [redacted]

- [redacted]

It was concluded that the toxicology studies support progression into clinical trials in healthy subjects.

5.2.3 Clinical studies

5.2.3.1 Effects in Humans

EDP- 938 is being evaluated in an ongoing Phase 1, randomized, double-blind, placebo-controlled, first-in-human (FIH) study in which the safety, tolerability, and PK is being assessed in healthy adult subjects. The Phase 1 study included a SAD phase enrolling a total of 6 dose cohorts of which, one was a two-part Food Effect (FE) cohort, and a MAD phase enrolling 5 dose cohorts.

[redacted]

[redacted]

In summary:

- [redacted]
- [redacted]

These results support further clinical evaluation of EDP-938 in patients with RSV.

For a detailed description of available clinical data, please refer to the EDP-938 IB addendum.

5.3 Rationale for the study

EDP-938 is an investigational drug substance being developed for the treatment of RSV infection.

EDP-938 is a novel non-fusion replication inhibitor of RSV, and it is against all RSV A and B laboratory strains and clinical isolates tested *in vitro*. In the primary human bronchial epithelial cells, EDP-938 had an EC_{50} of 21nM, 23nM and 64nM, against RSV-A Long, M37 and RSV-B Washington strains, respectively. EDP-938 appears to inhibit RSV replication by modulating viral nucleoprotein (N), based on *in vitro* resistance studies, although the exact mechanism of action is under further investigation. EDP-938 has demonstrated *in vivo* efficacy in the RSV infected African Green Monkey model.

The rationale for taking EDP-938 into further development is the expectation that this compound could be effective for the treatment of RSV, to address the unmet medical need for more effective antiviral therapies for RSV.

5.3.1 Study design

The study will be conducted by hVIVO Services Limited, which has extensive experience with viral challenge studies. Numerous studies have been performed using experimental RSV-A Memphis 37b infection in human subjects. To date, in hVIVO's studies, more than 900 subjects have been successfully and safely inoculated with RSV-A Memphis 37b. These studies[42-47] demonstrated that adults could be infected by nasal inoculation. This strain has been shown to cause symptoms and virus shedding that closely match natural infection.

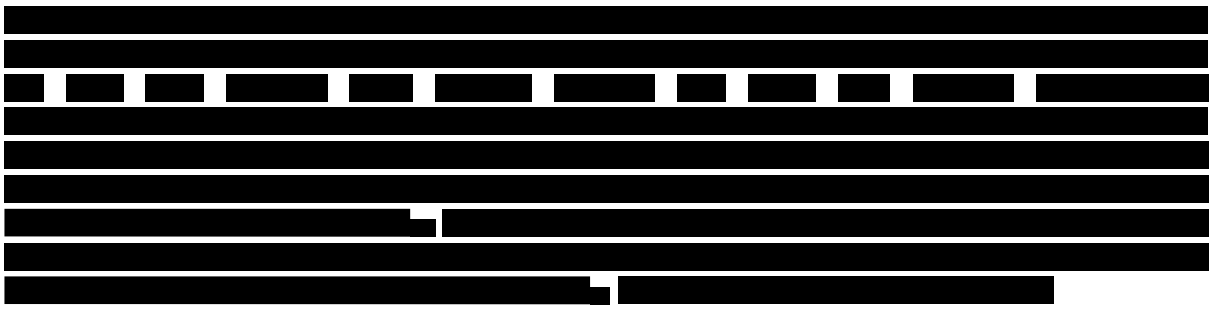
Administration of study drug and challenge with RSV-A Memphis 37b will take place in hVIVO's specialised Unit. Standard study procedures (including collection of blood, urine, and nasopharyngeal secretions for assessment of safety and efficacy) have been employed in previous studies conducted by hVIVO.

5.3.2 EDP-938 dose regimen

Doses selected for Part 1 of the Study are:

- 600mg OD every 24 hours (+/- 1hr) for 5 days
- A single Loading Dose (LD) of 500mg followed by a 300mg dose every 12 hours (+/- 1hr) for 5 days.

These doses are expected to provide exposures in the anticipated therapeutic range.



Based on in vitro testing, an EC_{90} value for EDP-938 of 20 ng/ml was determined in human bronchial epithelial cells (HBEC). The EDP-938 doses selected for Part 1 (600mg OD or a single LD of 500mg followed by 300mg dose every 12 hours) are expected to result in mean C_{trough} concentrations at steady state of approximately 600ng/ml. These values are expected to provide mean exposures of approximately 30x compared to the EC_{90} in HBEC (based on total EDP-938 concentrations). As EDP-938 is 95% plasma protein bound, the corresponding multiple corrected for plasma protein binding is approximately 1.5x for both dosing regimens.

Doses and regimens for Part 2 of the Study will be determined based on emerging PK, virology, clinical symptom score and safety data from Part 1. However, the maximum individual dose in any treatment regimen will not exceed a loading dose followed by maintenance doses which are projected to deliver mean IMP exposure of 28745 ng.hr/mL (AUC).

5.4 Potential risks and benefits to participants

There are no expected benefits to study participants, although subjects may develop some immunity to RSV-A Memphis 37b and benefit from a general health check at screening.

The known risks to participants are detailed below. However, there may also be risks that are unforeseen and not anticipated (e.g., unknown allergies). Every effort will be made to monitor the health of the subjects to ensure that such risks are minimised. Trained medical personnel and facilities will be available to provide medical emergency care.

5.4.1 Virus

Subjects have approximately 65% to 85% chance of becoming infected with RSV following the administration of the virus[6]. Typical RSV illness is characterised by an abrupt onset of rhinitis, nasal stuffiness, fever, malaise, myalgia (muscle aches), and sore throat. In healthy adults, the illness usually resolves without any treatment, with relief of symptoms occurring naturally within 7 to 10 days. Qualified doctors and nurses in the Quarantine Unit will manage any symptoms.

The study virus, like many viruses, can cause more substantial health issues such as myocarditis (inflammation or damage to the heart muscle). However, the chance of this resulting in serious or permanent changes is rare, as most cases are minor and resolve without any lasting changes. In hVIVO's virus challenge studies, uncommonly blood tests have shown a change suggestive of myocarditis, although in these few subjects the blood tests returned to normal without treatment and were not associated with specific symptoms or ECG changes. Severe complications of naturally occurring RSV infection tend to occur almost exclusively in infants, the elderly, and persons of any age with chronic co-morbidities and significant immune compromise.

It is unlikely for the subjects to transmit RSV to their close contacts. After infection with RSV, the virus will be present in the subjects' noses for several days; although it is not expected that infectious RSV will be present in the respiratory tract at the time of discharge from the isolation facility (quarantine). This is because the usual duration of time that RSV infection remains in adults is several days shorter than the time subjects spend in the isolation facility (quarantine). A nasal swab sample will also be tested for RSV prior to discharge using a qualitative RSV Rapid Viral Antigen Test (RVAT) to determine subjects' suitability for departure. If a subject is still positive for RSV (using RVAT) on Day 12, he/she may be asked to remain in quarantine. A further test will be carried out on Day 12 evening, if negative the

subject can be discharged. If the test is still positive on Day 12 or 13 and following review by the Investigator, the subject may be asked to remain in quarantine for further observation.
If symptoms are present, but no virus is detected (negative RVAT), discharge will be at the investigator's discretion. If appropriate, subjects may reside in quarantine for extra days if required.

5.4.1.1 Vulnerable populations

To reduce the risk of passing the Challenge Virus to others, subjects will be asked to avoid contact (have close contact or share the same apartment or house) with vulnerable people for 2 weeks after they leave quarantine. For the purposes of this protocol, a vulnerable individual includes but not limited to the following:

- Persons ≥65 years of age.
- Children ≤2 years of age.
- Residents of nursing homes.
- Persons of any age with significant chronic medical conditions such as:
  - Chronic pulmonary disease (e.g., severe asthma, COPD).
  - Chronic cardiovascular disease (e.g., cardiomyopathy, congestive heart failure, cardiac surgery, 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, hemoglobinopathies).
  - Immunosuppression or cancer.
  - Neurological and neurodevelopmental conditions (e.g., cerebral palsy, epilepsy, stroke, seizures).
- Individuals who are receiving long-term aspirin therapy.
- Women who are pregnant or who are trying to become pregnant.

5.4.2 EDP-938

Based on pre-clinical data and final unblinded data for the SAD part and preliminary blinded data for the MAD part of the ongoing FIH Study EDP- 938-001, EDP-938 is expected to be safe and well tolerated in subjects inoculated with RSV.

[redacted]

5.4.3 Study procedures

Some of the study procedures may cause discomfort to the subject, however these normally resolve without further problems. The discomforts due to study procedures are described in the Volunteer Information Sheet (VIS).

The blood tests performed to address the health of the subjects at screening and during the study may indicate that a subject has an infection that he/she was not previously aware of (such as HIV or hepatitis) or an unexpected illness. The hVIVO doctor will provide the subject's general practitioner (GP), or doctor with a referral letter if the subject agrees. There may also

be circumstances in which disclosing information without consent is justified in the public interest for important public benefits as required by local regulations.

Should any new information relevant to the subjects' participation in the study and their safety become available, a member of the hVIVO medical staff will notify subjects in a timely manner. If appropriate, subjects will be asked to reconfirm their consent to their participation in the study.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Primary Objective

To evaluate the antiviral activity of EDP-938 compared to placebo in healthy adult subjects inoculated with RSV-A Memphis 37b.

6.1.1 Primary Endpoint

The area under the curve (AUC) for RSV viral load measured in nasal washes by quantitative reverse transcription polymerase chain reaction (RT-qPCR), in subjects inoculated with RSV-A Memphis 37b.

6.2 Secondary Objectives

- To evaluate EDP-938 compared to placebo in healthy adult subjects inoculated with RSV-A Memphis 37b in terms of:
    - Clinical symptoms
    - Viral load
    - Safety and Tolerability
- To characterise the PK profile of multiple doses of EDP-938 and metabolites in healthy adult subjects inoculated with RSV-A Memphis 37b.
- To characterise the relationship between Plasma PK of EDP-938 and viral load AUC (RT-PCR) and total symptom score AUC

6.2.1 Secondary Endpoints

Secondary endpoints relating to efficacy include, but not limited to:

6.2.1.1 Efficacy

- Clinical Symptoms:
    - Effect of EDP-938 compared to placebo on RSV symptoms (using the 10- item diary card), with endpoints including:
        - AUC of total symptom score
        - Peak total symptom score over the duration of quarantine
        - Total symptom score
        - Time to peak symptom score after IMP dosing.
        - Time to resolution from peak symptom.
    - Total weight of nasal mucus produced (via weighed paper tissues).
- Viral Load:
    - Additional viral load endpoints calculated separately using data from RT-qPCR of nasal wash comparing placebo and EDP-938 treated including:

- Peak viral load
- Time to peak viral load
- Time to resolution from peak
- Time to cessation of virus quantifiable post first dosing

6.2.1.2 Safety

Secondary endpoints relating to safety include, but are not limited to:

- AEs
- Physical Examinations
- Vital signs
- 12-lead ECGs
- Spirometry
- Clinical laboratory results (including biochemistry, haematology, coagulation (if required), cardiac enzymes and urine analysis

6.2.1.3 Pharmacokinetics

Secondary endpoints related to PK include, but are not limited to:

- Plasma PK parameters of EDP-938 (and metabolites) following repeat dose administration in healthy adult subjects inoculated with RSV-A Memphis 37b: C_{max}, T_{max}, $t_{1/2}$, CL/F, λ_z, Vd/F, C12, C24, AUC_{last}, $AUC_{0\text{-}tau}$, or $AUC_{0\text{-}inf}$ (as applicable).
- Plasma PK (AUC) correlations with viral load AUC (e.g. RT-PCR) and TSS AUC

6.3 Exploratory Objectives

- [redacted]

6.3.1 Exploratory Endpoints

[redacted]

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

[redacted]

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

[redacted]

7 STUDY POPULATION

7.1 Study Population

Subjects will be healthy males and/or females, 18 to 55 years of age, who meet the eligibility criteria outlined in Section 7.3 and 7.4.

The study staff will not enter any subjects into the study prior to the provision of written informed consent by each subject. All subjects that sign the study specific Informed Consent Form (ICF) will be added to the study screening/enrolment log.

A subject's status will be recorded as 'enrolled' only when he/she has been randomised, dosed, or inoculated [whichever occurs first].

A subject will be considered to have 'completed' the study after he/she has attended the last scheduled study visit (any one of the visits listed in Table 9.1 or the last unscheduled visit, as applicable).

7.2 Number of subjects

The study will consist of 2 (two) parts, and the number of subjects are as outlined below:

- Part 1:
  - 114 subjects will be inoculated with RSV-A Memphis 37b, of which 76 subjects will complete dosing with EDP-938 (38 subjects in each of 2 EDP-938 treatment groups) and 38 subjects will complete dosing with placebo.
- Part 2:
  - Up to a maximum of 84 subjects in total for Part 2 will be enrolled following an analysis of Part 1. Subjects will be inoculated with RSV-A Memphis 37b, of which up to 63 subjects will complete dosing with EDP-938 and up to 21 subjects will complete dosing with placebo.

Eligible subjects may be invited to attend quarantine as reserves for each group. If a subject no longer complies with the study eligibility criteria, the subject discharged on or before Day 0 (prior to inoculation) and may be replaced with a reserve subject.

7.3 Inclusion criteria

NO	INCLUSION CRITERIA
1	Aged 18 to 55 years from the day *prior to* signing the consent form.
2	In good health with no history of major medical conditions that will interfere with subject safety, as defined by medical history, physical examination, and routine laboratory tests and determined by the Investigator at screening evaluation.

NO	INCLUSION CRITERIA
3	Subjects will have a documented medical history either prior to entering the study and/or following medical history review with the study physician at screening.
4	A total body weight ≥ 50 kg and Body Mass Index (BMI) ≥ 18 kg/m^2 and ≤ 30kg/m^2.
5	The following inclusion criteria are applicable to subjects participating in the study: • Female subjects must have a negative pregnancy test at screening and prior to viral challenge. • Female subjects of **childbearing potential** must use **one form** of highly effective contraception. Hormonal methods must be in place from at least 2 weeks prior to entry to quarantine. The contraception use must continue until 90 days after the date of Viral Challenge/last dosing with IMP (whichever occurs last). Highly effective contraception is as described below: - Established (a minimum of 2 weeks prior to admission) use of hormonal methods of contraception described below. ▪ combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: • oral • intravaginal • transdermal ▪ progestogen-only hormonal contraception associated with inhibition of ovulation: • oral • injectable • implantable Note: when hormonal methods of contraception are used, male partners are required to use a condom with a spermicide. - intrauterine device (IUD) - intrauterine hormone-releasing system (IUS) - Bilateral tubal ligation - Male sterilisation (with the appropriate post vasectomy documentation of the absence of sperm in the ejaculate) where the vasectomised male is the sole partner for that woman. - 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 subject. • Female subjects who are no longer of child bearing potential.

NO	INCLUSION CRITERIA
	- Women no longer of child bearing potential (post-menopausal females are defined as having a history of amenorrhea for at least 2 years, otherwise they should have documented status as being surgically sterile or post hysterectomy. The latter applies only to females participating in the study). • Male subjects must agree to the contraceptive requirements below at entry to quarantine and continuing until 90 days after the date of Viral challenge / last dosing with IMP (whichever occurs last). - 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. - Male sterilisation with the appropriate post vasectomy documentation of the absence of sperm in the ejaculate (*please note that the use of condom with spermicide will still be required to prevent partner exposure).* This applies only to males participating in the study. - In addition, for female partners of child bearing potential, that partner must use another form of contraception such as one of the highly effective methods mentioned above for female subjects. - 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 subject. In addition to the contraceptive requirements above, male subjects must agree not to donate sperm following discharge from quarantine until 90 days after the date of Viral Challenge/last dosing with IMP (whichever occurs last).
6	An informed consent document signed and dated by the subject and the Investigator.
7	Sero-suitable to the challenge virus. • The serology result obtained suggests that the subject is sensitive to RSV infection, i.e. they are likely to be infected following inoculation with the challenge virus.
8	Subjects who have experienced no more than one mild episode of wheeze (mild is defined as having been treated with bronchodilators only) after the age of 12, may be included at the Investigator's discretion, providing the episode lasted no more than 2 weeks, and ended more than 1 year ago. A history of childhood asthma up to and including the age of 12 years is acceptable.

7.4 Exclusion criteria

NO	EXCLUSION CRITERIA
1	subjects 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]). • Of those subjects that have smoked <10 pack years at any time, a subject will be excluded if, in the last month (i.e. 30 days) prior to admission, they have used tobacco in any form (e.g. smoking or chewing) or other nicotine-containing products in any form (e.g. gum, patch and electronic cigarettes).
2	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/first dosing with IMP (whichever occurs first).
3	• Any history or evidence of any clinically significant or currently active cardiovascular, respiratory, dermatological, gastrointestinal, endocrinological, haematological, hepatic, immunological (including immunesuppression), metabolic, urological, renal, neurological, or psychiatric disease (including subjects with a history of depression and/or anxiety with associated severe psychiatric comorbidities, for example psychosis; subjects with a history of depression of any severity within the last 2 years should only be included if the PHQ-9 score is less than or equal to 4) • And/or other major disease that, in the opinion of the Investigator, may interfere with a subject completing the study and necessary investigations. • The following conditions apply: • Subjects with clinically mild atopic eczema/atopic dermatitis and clinically mild psoriasis may be included at the Investigator's discretion (e.g., if small amounts of regular topical steroids are used, no eczema in cubital fossa; moderate to large amounts of daily dermal corticosteroids is an exclusion). • Subjects with a physician diagnosed underactive thyroid who have been controlled on treatment for at least 6 months with evidence of a normal thyroid function test (TFT) can be included at the discretion of the PI. • Rhinitis (including hay fever) which is clinically active or history of moderate to severe rhinitis, or history of seasonal allergic rhinitis likely to be active at the time of inclusion into the study and/or requiring regular nasal corticosteroids on an at least weekly basis, within 30 days of admission to quarantine will be excluded. Subjects with a history of currently inactive rhinitis (within the last 30 days) or mild rhinitis may be included at the PI's discretion. • Any concurrent serious illness including history of malignancy that may interfere with the aims of the study or a subject completing the study.

NO	EXCLUSION CRITERIA
	Basal cell carcinoma within 5 years of initial diagnosis or with evidence of recurrence is also an exclusion. • Subjects reporting physician diagnosed migraine can be included as long as there are not associated neurological symptoms such as hemiplegia or visual loss. Cluster headache/migraine or prophylactic treatment for migraine is an exclusion.
4	A forced expiratory volume in 1 second (FEV1) < 80%.
5	Subjects with any history of physician diagnosed and/or objective test confirmed asthma, COPD, pulmonary hypertension, or chronic lung condition of any aetiology.
6	Positive human immunodeficiency virus (HIV), active hepatitis A (HAV), B (HBV), or C (HCV) test.
7	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).
8	Any clinically significant history of epistaxis (large nosebleeds) within the last 3 months and/or history of being hospitalized due to epistaxis on any previous occasion.
9	Any nasal or sinus surgery within 3 months of Viral Challenge.
10	Twelve-lead ECG recording with clinically relevant abnormalities as judged by the study physician/PI.
11	Confirmed positive test for drugs of abuse on admission.
12	Venous access deemed inadequate for the phlebotomy and cannulation demands of the study.
13	Presence of fever, defined as subject presenting with a temperature reading of ≥ 37.9 ºC on Day -2, Day -1, and/or pre-Challenge on Day 0.
14	a) Evidence of vaccinations within the 4 weeks prior to the planned date of Viral Challenge/first dosing with IMP (whichever occurs first). 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).

NO	EXCLUSION CRITERIA
15	Those employed or immediate relatives of those employed at hVIVO or the Sponsor.
16	Receipt of blood or blood products, or loss (including blood donations) of 470 mL or more of blood during the 3 months prior to the planned date of Viral Challenge/first dosing with IMP (whichever occurs first) or planned during the 3 months after the final visit.
17	Use within 7 days prior to the planned date of Viral Challenge/first dosing with IMP (whichever occurs first) of any medication or product (prescription or over-the-counter), for symptoms of hay fever, dermatitis, nasal congestion or respiratory tract infections including the use of regular nasal or dermal corticosteroids or antibiotics, apart from those described and allowed in exclusion criteria 3.
18	a) Receipt of any investigational drug within 3 months prior to the planned date of Viral Challenge/first dosing with IMP (whichever occurs first). b) Receipt of three or more investigational drugs within the previous 12 months prior to the planned date of Viral Challenge/first dosing with IMP (whichever occurs first). 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 12 months taken from the date of Viral Challenge/first dosing with IMP (whichever occurs first) in the previous study to the date of expected Viral Challenge in this study.
19	Receipt of systemic (intravenous and/or oral) glucocorticoids or systemic antiviral drugs within 6 months prior to the planned date of Viral Challenge/first dosing with IMP (whichever occurs first).
20	History or currently active symptoms suggestive of upper or lower respiratory tract infection within 6 weeks prior to viral challenge.

NO	EXCLUSION CRITERIA
21	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 Principal Investigator, the medication will not interfere with the study procedures or compromise subject safety. Specifically, the following are excluded: • Herbal supplements within 7 days prior to the planned date of Viral Challenge. • Chronically used medications, vitamins or dietary supplements, including any medication known to be moderate / potent inducer or inhibitor of CYP450 enzymes/P-gp/BCRP, within 21 days prior to the planned date of Viral Challenge. • 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)
22	History of anaphylaxis-and/or a history of severe allergic reaction or significant intolerance to any food or drug, as assessed by the PI.
23	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).
24	Any other finding that, in the opinion of the Investigator, deems the subject unsuitable for the study.

7.5 Discontinuation of a subject's participation

7.5.1 Subject withdrawal

A subject may withdraw their consent to participate in the study at any time, for any reason, without prejudice to his/her future medical care. Subjects may decline to give a reason for their withdrawal.

Additionally, the Principal Investigator may withdraw a subject if, in their clinical judgement, it is in the best interest of the subject or if the subject cannot comply with the protocol. Wherever possible, the tests and evaluations listed for the Early Withdrawal visit should be carried out, and if clinically indicated, the subject 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 subject would be referred to his/her GP.

Subjects will be counselled that early withdrawal from the viral challenge phase of the study is strongly discouraged, as it may pose a risk both to the subject and his/her contacts. In the event of a subject insisting on early withdrawal during the challenge isolation period, the subject will be encouraged to stay and would be advised of the potential risks of carrying RSV-A Memphis 37b infection into the community, and to vulnerable groups (5.4.1.1) in particular.

7.5.2 Subject discontinuation

A subject's participation may be stopped (early discontinuation) for any of the following reasons:

- Non-compliance with the study requirements and restrictions.
- Clinically significant abnormal laboratory findings, which in the opinion of the Investigator(s) and/or Sponsor, precludes further participation in the study.
- Development of inter-current illness which, in the opinion of the Investigator would compromise the health of the subject or the study objectives.
- The Investigator’s decision that withdrawal from further participation would be in the subject’s best interest.
- Termination of the study at the discretion of the Investigator(s) or Sponsor for safety, behavioural, or administrative reasons.
- The wish of the subject.

Subjects who are withdrawn from the study, will be requested to attend an Early Withdrawal Visit, with assessments as detailed in Table 9-1.

7.5.3 Replacements

Subjects that have been inoculated but not dosed will be replaced.

Subjects who have been dosed with IMP (i.e. subject has received at least one IMP dose) and end participation early will not be replaced.

7.5.4 Pregnancy

In the event of a subject discontinuing the study prematurely due to pregnancy, or if pregnancy in a study subject’s partner becomes known, please refer to section 15 for pregnancy reporting requirements.

7.5.5 Arrangements for additional care if required

Subjects who still have significant worsening of their clinical signs compared to baseline may be required to stay in quarantine for additional observation and medical management longer than the scheduled Day 12 discharge date. Assessments will be conducted as clinically indicated by the Investigator. Such subjects upon discharge may be asked to return for a follow-up visit whether that be at the scheduled day 28 or an unscheduled visit.

7.6 Reserve subjects

Reserve subjects may remain available to replace any subjects who become ineligible for the study between the day of admission to quarantine and the final assessment of eligibility prior to Viral Challenge.

Reserve subjects who are not needed for a particular quarantine group may be discharged from the planned quarantine before or on the day of Viral Challenge (Day 0) at the latest.

A reserve subject who was not enrolled into a quarantine group may be enrolled into a later quarantine group within 56 days of screening with no re-screening required if the Day - 2 (or Day -1) clinical assessments meet the eligibility criteria, and provided sero-susceptibility results are within the 90 days (inclusive) window from the planned inoculation date (Day 0).

7.7 Subject numbering

hVIVO assigns a unique subject number to each subject in the hVIVO subject database. This subject number will be used to identify a subject up to the point of randomisation (Section 10.1), on source documents, on all study correspondence and in the study database.

A separate randomisation number will be allocated to the subjects at randomisation and will be used for allocation of IMP.

For subjects who subsequently do not enter the study, a reason will be documented in the source documentation and the subject's medical notes.

For subjects who are subsequently enrolled into the study, the Investigator will maintain an enrolment log, listing the identifiers for each subject alongside the subject number assigned and the date enrolled. A copy of the log will be filed in the hVIVO TMF at the study site.

8 PROCEDURES FOR MONITORING SUBJECT COMPLIANCE WITH TREATMENT AND RESTRICTIONS

8.1 Concomitant therapies

All medications taken from the time the subject consents to participation in the study will be recorded. Concomitant medications taken during the quarantine stage will be stored, prescribed and administered in line with their label-specific requirements and full accountability will be maintained. Any medications taken and changes in medications during the study up to final study contact Day 28 (±3 days) will be recorded in the source data.

- All medications must be stopped prior to the planned date of dosing with IMP/viral challenge (whichever occurs first) unless in the opinion of the Investigator and/or Sponsor's Medical Monitor, the medication will not interfere with the study procedures or compromise subject safety. Specifically, the following are excluded:

- Herbal supplements within 7 days prior to the planned date of Viral Challenge.

- Chronically used medications, vitamins or dietary supplements, including any medication known to be an inducer or inhibitor of CYP450 enzymes, within 21 days prior to the planned date of viral challenge.

- Over-the-counter (OTC) 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).

During the quarantine, the 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.

Use of all concomitant medications will be recorded in the subject's source notes, including all details/parameters that are required by the clinical database. This will include all prescription drugs, herbal preparations, and OTC medications.

Any concomitant medication required for the subject's welfare may be given by the Investigator. However, it is the responsibility of the 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.

8.1.1 Prohibited Medications:

Medications which are prohibited throughout the study are shown in Table 8-1 below.

Table 8-1: Prohibited medications

Prohibited medication	Washout
Systemic corticosteroids (oral and parenteral) therapy for any reason is not allowed in this group.	6 months prior to Day 0 (Inoculation).
Systemic (oral and parenteral) antiviral drugs.	6 months prior to Day 0 (Inoculation).
Vaccinations: Intention to receive any vaccination(s) with the exception of flu vaccinations before the Day 28 Follow-up Visit; (no travel restrictions will apply after the Day 28 Follow-up Visit).	4 weeks prior to the planned date of viral challenge.
Use or anticipated use during conduct of the study of concomitant medications (prescription and non-prescription), including vitamins or herbal and dietary supplements within the specified windows, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise subject safety.	Herbal supplements within 7 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 CYP450 enzymes, (CYP450) enzymes/P-gp/BCRP, within 21 days prior to the planned date of viral challenge.
Short and long-acting anti-histamines, and mast cell stabilisers (including inhaled sodium cromoglycate or nedocromil).	7 days prior to Day -2/ Day -1.
Any medication or product (prescription or over-the-counter), for symptoms of nasal congestion or respiratory tract infections including the use of nasal steroids.	Within 7 days prior to the planned date of viral challenge.
History of immunotherapy or concurrently undergoing immunotherapy treatment.	Prohibited.
Receipt of any systemic chemotherapy agent, immunoglobulins, or any other cytotoxic or immunosuppressive drugs at any time.	Prohibited.

8.1.2 Permitted medications

Medications which are permitted throughout the study are shown in Tables 8-2 below.

Table 8-2: Permitted medications

Permitted medication	Details
Paracetamol.	Maximum 4g daily dose from 7 days prior to planned date of inoculation and throughout the study duration.
Oral contraceptives.	Allowed at any time during the study.
OTC or prescribed medications not listed in prohibited medications are subject to approval by the PI.	

8.2 Strenuous Exercise

Subjects must refrain from strenuous exercise for 72 hours prior to blood draws at clinic visits, during confinement in the Quarantine unit, and until their last study visit (unless it is within the usual activity of the subject) in order to avoid potential spurious changes in clinical laboratory safety parameters.

8.3 Alcohol, drugs of abuse and tobacco

Subjects must not consume alcohol for 3 days prior to entry to the Quarantine Unit, for the entire quarantine period and for 72 hours prior to any clinic visits. Subjects must not smoke or otherwise use tobacco products in the last month (i.e. 30 days) prior to viral challenge and the entire study period.

Subjects must not use recreational drugs or legal highs during the study (from Screening Visit until follow up visit).

Alcohol and drugs of abuse testing will be conducted during the study and must be negative at all times. Action is at PI's discretion if positive.

The requirements for contraceptive measures are outlined in the study eligibility criteria (Section 7.3).

8.4 Restrictions related to study assessments

8.4.1 Spirometry

Subjects must abstain from methylxanthine-containing beverages or food (e.g. coffee, tea, cola, and chocolate) for 48 hours before and during quarantine, and prior to all visits requiring spirometry.

9 STUDY DESIGN

9.1 Summary

This is a randomised, Phase 2a, double-blind, placebo-controlled study in healthy subjects challenged with RSV-A Memphis 37b.

The study is divided into 2 parts:

- In Part 1:
  - 5 consecutive days of dosing in three treatment groups, dosing BD to maintain the blind. Active doses administered OD (every 24 hours (±1 hour) interval) or as a single loading dose followed by BD (every 12 hours (±1 hour) interval) for a total 10 doses respectively of either:
    - Group 1: Placebo (n=38); subjects in this group will receive placebo dose BD (every 12 hours (±1 hour) interval) for a total of 10 doses.
    - Group 2: EDP-938 oral [redacted] loading dose group (n=38): subjects in this group will receive 500mg first dose, and at 12 hours (±1 hour) interval receive 300mg second dose, then 300mg doses BD for a total of 10 doses.
    - Group 3: EDP-938 oral [redacted] 600mg dose group (n=38): subjects in this group will receive a daily 600mg dose followed by a placebo dose at 12 hours (±1 hour) interval for a total of 10 doses.

  - IMP dosing to start on confirmation of positive result by qualitative integrated cycler polymerase chain reaction (qicPCR) on nasal wash. Nasal wash for qicPCR will be performed BD on Study Days 2-5 (Study Day 5 morning only), or until a positive result is achieved, whichever is sooner.

  - Earliest start of IMP dose will be in the evening on Study Day 2 post viral challenge (IMP will be initiated 12 ± 1-hour post nasal wash confirmation of a positive qicPCR result).

    OR

  - Dosing will start in the evening of Study Day 5 if no positive result is obtained by qicPCR.

- In Part 2:

  - Up to a maximum of 84 subjects in total for Part 2 will be enrolled following an analysis of Part 1. Up to 63 subjects will complete dosing with EDP-938 and up to 21 subjects will complete dosing with placebo.
  - The dose(s) of EDP-938 selected will be projected to deliver an efficacious exposure and will be based on emerging PK, PK/PD modelling, virology, clinical symptom score and safety data. [redacted]
  - In Part 2, 63 subjects will be randomised equally into 1 of 3 treatment groups as below. Additional treatment groups may be evaluated, however, the maximum number of subjects enrolled in Part 2 will be 84.
    - Group 1 (n=21): Placebo dosed BD for 5 days, with dosing at 12 hours (± 1 hour) interval
    - Group 2 (n=21): A single Loading Dose of 400mg (Dose 1), followed by 200mg second dose at 12 hours (± 1-hour interval), then 200mg doses BD, and with dosing for 5 days,

- Group 3 (n=21): A single Loading Dose of 600mg (Dose 1), followed by a 300mg dose OD (every 24 hours (±1 hour) interval) dosing, and with dosing for 5 days.

- In order to maintain the study blind, subjects in the active OD dosing group will have their regimen supplemented by the administration of a placebo matched to EDP-938 in order to mimic the BD dosing group.

The study is divided into the following 3 study phases:

Study phase	Procedures
Screening phase	Attend Screening Visit from -56 to Day -3 prior to challenge. • Historical pre-screening data collected through the hVIVO generic screening process within 56 days to 3 days prior to inoculation (90 days for viral serology) may be used for screening procedures. Historical pre-screening data obtained prior to this window can be re-assessed any time within 56 days to 3 days prior to Inoculation.
Quarantine and challenge phase	• Admission to Quarantine Unit • Inoculation with Challenge Virus • Administration of the IMP • Study procedures and assessments • Discharge

Follow-up phase	Part 1: Follow-up Visit • Study Day 28 [± 3 days] and study termination Part 2: Follow-up Visit • Study Day 13, where applicable (only subjects who started IMP dosing on the evening of Study Day 5 (up to Day 8 evening) will return for a PK sample on Study Day 13) • Study Day 14, where applicable (only subjects who started IMP dosing on the evening of Study Day 5 (up to Day 8 evening) will return for a PK sample on Study Day 14) • Study Day 15, where applicable (only subjects who started IMP dosing on the evening of Study Day 5 (up to Day 8 evening) will return for a PK sample on Study Day 15) • Study Day 28 [± 3 days] and study termination

The overall study design is depicted in Figure 9-1.

9.1.1 Part 2 Progression and Additional Evaluation Guidelines

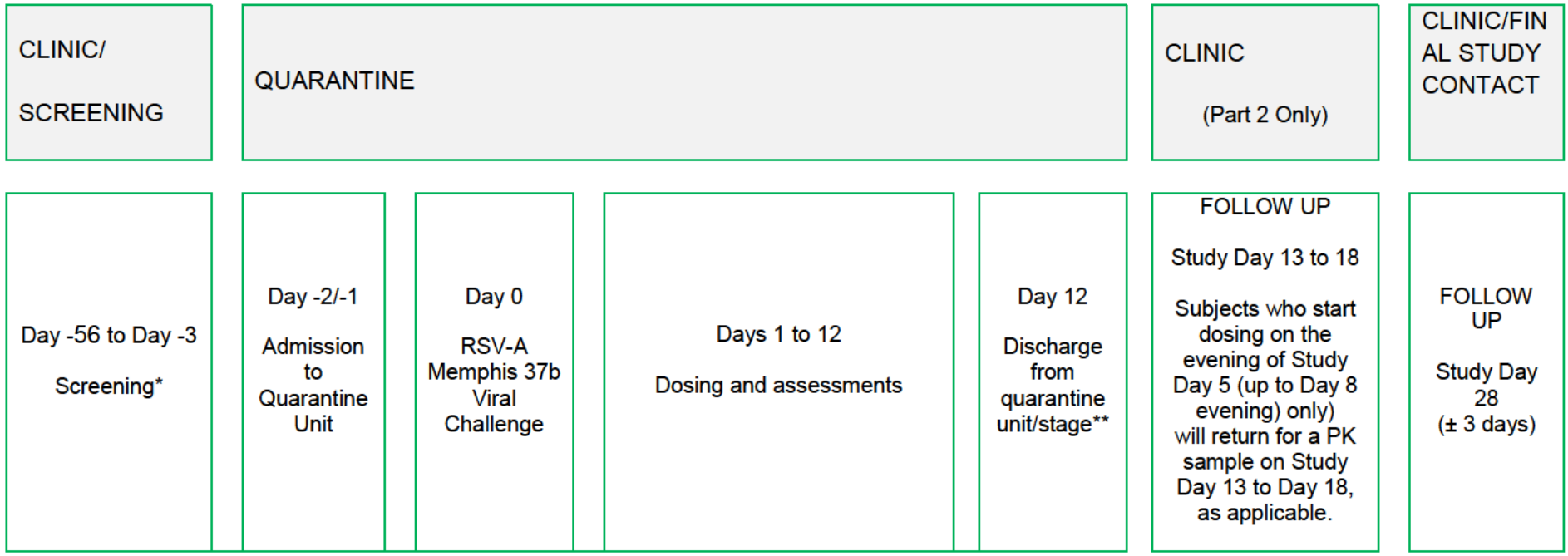
Part 2 will commence no earlier than after an evaluation by the Sponsor and Investigator of the virology, clinical symptom score, PK, and safety data from Part 1.

Prior to Part 2, the Sponsor will review the emerging data to confirm dose(s) (up to 600mg dose) and dose frequencies (OD or BD) to be evaluated in Part 2. Higher doses may be evaluated in the event that there is the potential for additional antiviral responses; [redacted] and an acceptable safety profile is observed. Lower doses may be evaluated in the event that a degree of viral suppression is observed. A longer duration of dosing (up to 7 days maximum) may be evaluated if there is evidence of incomplete viral suppression or viral rebound after completion of therapy, and an acceptable safety profile is observed. See section 18.5.1 for stopping criteria.

[redacted]

The maximum duration of treatment in parts 1 & 2 will not exceed 5 days and 7 days respectively.

Figure 9-1: Study design



* Attend Screening Visit from -56 to Day -3 prior to challenge. Historical pre-screening data collected through the hVIVO generic screening process within 56 days to 3 days prior to inoculation (90 days for viral serology) may be used for screening procedures. Historical pre-screening data obtained prior to this window can be re-assessed any time within 56 days to 3 days prior to Inoculation.

**If a subject is still positive for RSV (using RVAT) on Day 12, he/she may be asked to remain in quarantine. A further test will be carried out on Day 12 evening, if negative the subject can be discharged. If the test is still positive on Day 12 or 13 and following review by the Investigator, the subject may be asked to remain in quarantine for further observation. If symptoms are present, but no virus is detected (negative RVAT), discharge will be at the investigator's discretion. If appropriate, subjects may reside in quarantine for extra days if required.

The timing of study procedures relative to each phase is shown in Section 9. The procedures and assessments which will be undertaken to evaluate safety and efficacy are described in Section 13: Assessments and Procedures.

Subjects will:

- Attend Screening Visit from -56 to Day -3 prior to challenge
- Be admitted to the Quarantine Unit on Day -2/-1
- Be inoculated with Challenge Virus on Day 0
- Be discharged from the Quarantine Unit on Day 12 (if necessary, subjects may reside in quarantine for a further night or longer before discharge)
- Return to the clinic on Study Day 13, 14, 15, 16, 17 and 18, as applicable (subjects who start IMP dosing in the evening of study Day 5 (up to Day 8 evening) will return for a PK sample.
- Return to the clinic for a Follow-up Visit(s) on Day 28 (± 3 days) (all subjects).

The duration of a subject's participation from Screening Visit to the scheduled Follow-up Visit(s) on Day 28 (± 3 days) will be approximately 3 months.

The total duration of the clinical phase of the study, from the start of subject screening to the last subject's last visit (LSLV) is expected to be approximately 18 months.

9.2 Screening Visit

Subjects who are sero-suitable for the challenge virus (screened through the hVIVO generic screening process) will be invited to attend a Screening Visit within 56 days to 3 days prior to viral challenge.

Historical generic screening data collected through the hVIVO generic screening process within 56 days to 3 days prior to inoculation (90 days for viral serology) may be transferred to the study after the study specific consent form has been signed by the trial participant. Historical pre-screening data obtained prior to this window can be re-assessed any time within 56 days to 3 days prior to viral challenge.

9.2.1 Informed consent procedure

The Investigator will obtain a signed ICF from each subject before any study specific procedures are performed.

When historical screening data collected through the hVIVO generic screening process is used for screening, the study specific ICF will be obtained at quarantine admission (Day -2/-1) from each subject before any study specific procedures are performed.

Potential subjects will typically be sent a copy of the ICF when their Screening Visit/Quarantine admission visit (as applicable) is arranged and at least 24 hours 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 ICF is discussed by the Investigator, and they will be given the opportunity to ask any questions, and may take the information sheet away to consider their participation.

All subjects will be required to have a good understanding of English and the Investigator will be responsible for ensuring that the subject understands the information contained in the ICF. Once the Investigator has confirmed that the subject has understood the study, including the benefits and risks of participation, the subject and the Investigator can sign and date the ICF.

The ICF must be signed and dated by the subject and countersigned by the Investigator (whoever conducted the consent discussion). A copy of the ICF will be given to the subject, and the original will be held in the hVIVO TMF.

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

If the ICF is amended during the study, the PI/Investigator will follow all applicable regulatory requirements pertaining to approval of the amendment by the research ethics committee (REC). The site(s) must use the amended ICF for all new subjects and if required, the consent process will be repeated with the amended ICF for on-going subjects.

9.2.2 Screening Procedure

Screening assessments will be performed as detailed in Table 9-1 and may be repeated as necessary on admission to the hVIVO Quarantine Unit.

Results of tests or examinations performed under other ethically approved hVIVO protocols within 56 days to 3 days prior to viral challenge (90 days for viral serology) may be used to determine eligibility. Historical pre-screening data obtained prior to this window can be re-assessed any time within 56 days to 3 days prior to viral challenge. Serosuitability to the Challenge Virus may be reconfirmed at the PI/Investigator's discretion any time between the Screening Visit and the day of Viral Challenge. The subject will be excluded from the study if the results demonstrate that the subject is no longer serosuitable to the Challenge Virus. The specific virus neutralisation antibody titre used to determine subjects' serosuitability and the associated assay will be detailed in the Analytical Plan (AP).

9.3 Quarantine Phase

Subjects will be monitored closely throughout their stay in the Quarantine Unit; standard procedures will be performed as detailed in Table 9-1.

9.3.1 Admission

On Day -2 or Day -1, 2 or 1 days prior to the day of challenge, the subject will attend the Quarantine Unit; eligibility will be reviewed and a nasopharyngeal swab will be taken for respiratory pathogen screen (Section 13.14.1.1). Various study assessments and tests as detailed in Table 9-1 will be performed during this admission visit.

When historical screening data collected through the hVIVO generic screening process is used for screening, the study specific ICF will be obtained at quarantine admission (Day -2/-1) from each subject before any study specific procedures are performed.

If a subject is found to be ineligible based on review of the eligibility criteria, the subject will not proceed in that quarantine group. The Investigator/Study Physician will decide whether the subject should be permanently excluded from the study or invited back for repeat of assessments (i.e. repeat clinical laboratory test, if the initial screening assessments are still within the -56 to -3 window) or rescreening for a later quarantine, as appropriate .

Eligible subjects may be invited to attend quarantine as reserves for each group. If a subject no longer complies with the study eligibility criteria, the subject will be discharged and may be replaced with a reserve subject.

Subjects may be admitted to the Quarantine Unit on Day -1 at the Investigator's discretion.

Any assessments planned for Day -2 may be performed or repeated on Day -1.

During the Quarantine and Challenge phase, assessments and procedures will be performed as detailed in Table 9-1: Time and events schedule.

Viral Challenge is described in Section 11. EDP-938 dosing is described in Section 12.5.

9.3.2 Viral Challenge

If the subject remains eligible for the study, he/she will be inoculated with challenge virus on Day 0.

9.3.3 Discharge

On Day 12, subjects will be discharged from the Quarantine Unit if the nasopharyngeal swab sample, confirmed by rapid viral antigen test (RVAT), is negative for Challenge Virus. If a subject is still positive for RSV (using RVAT) on Day 12, he/she may be asked to remain in quarantine. A further test will be carried out on Day 12 evening, if negative the subject can be discharged. If the test is still positive on Day 12 or 13 and following review by the Investigator, the subject may be asked to remain in quarantine for further observation. If symptoms are present, but no virus is

detected (negative RVAT), discharge will be at the investigator's discretion. If appropriate, subjects may reside in quarantine for extra days if required.

Subjects may be discharged based on the subject's clinical condition and the PI/Investigator's assessment. If subjects are required to remain in quarantine longer than the scheduled day/time, all assessments will be at the discretion of the PI/Investigator. AEs and concomitant medications will be monitored.

Various study assessments and tests will be performed during this discharge day as detailed in Table 9-1.

9.4 Follow-up phase

The follow-up phase will commence once a subject has been discharged from the Quarantine Unit.

Further Follow-up Visits before Day 28 may be scheduled at the discretion of the PI/Investigator, if the subject has been symptomatic or require additional follow-up since discharge from the Quarantine Unit.

9.4.1 Study Day 13 to Day 18

Subjects who started IMP dosing on the evening of Study Day 5 (up to Day 8 evening) post Viral Challenge for up to 7 days dosing regimen in Part 2 will return for PK sampling on Study Day 13, 14, and 15, 16, 17 and 18 (as applicable) in order to obtain the PK sample(s) associated with the final dose of IMP, for the pre-dose, 0.5-hour,1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 8-hour, 10-hour, 12-hour, 15-hour, 24-hour, 30-hour, 36-hour, 48-hour, 60-hour, and 72-hour post final dose time points as applicable.

Other assessments performed at this Follow-up Visit (s) could include ECG, AE and ConMed review (in addition to the PK blood draw).

9.4.2 Day 28 (±3 days) Follow-up Visit

Subjects will return to the hVIVO clinic for 1 scheduled Follow-up Visit; at 28 days post-Viral Challenge (±3 days). Assessments will be performed as detailed in Table 9-1: Time and events schedule. For subjects lost to follow up, refer to Section 9.6.

Any AEs that are unresolved at the final Follow-up Visit may necessitate further unscheduled visits until the AE has resolved or the subject is deemed fit by the Investigator. Subjects may be discharged for GP follow-up if appropriate.

9.5 Duration of Subject Participation

The maximum duration of a subject's participation from screening to the last scheduled Follow-up Visit is expected to be approximately 3 months.

9.6 Lost to follow-up

In the event that a subject does not return or cannot be contacted for the final Follow-up Visit at Day 28 (±3 days) post-Viral Challenge, the Investigator will make every reasonable effort to contact the subject to review all AEs. In the event that a subject drops out of the study at any time, the reason for discontinuation, if known, must be fully documented in the source data. The site personnel will document the AEs and any other assessments and will make every effort to complete all required end of study assessments.

9.7 End of trial

The end of the trial is defined as the last subject's last scheduled visit (LSLV) at Day 28 (±3 days). If a safety visit is required after the last scheduled visit, this will be at the PI/Investigator's discretion as a duty of care, e.g., repeat spirometry or laboratory tests. These discretionary Follow-up Visits will not be considered part of the trial data unless they represent follow-up and closure on an AE or SAE identified during the trial period.

AEs that are unresolved at the Day 28 (±3 days) post-challenge Follow-up Visit may necessitate further Follow-up Visits if required.

9.8 Clinical Trial Summary Report

It is the Sponsor's (or Sponsor delegate) responsibility to send the Clinical Trial Summary Report to the REC and Medicines and Healthcare Regulatory Agency (MHRA) (if required) within 1 year of the end of the trial. In addition, the Sponsor or Sponsor delegate is responsible for entering appropriate data into the EudraCT results database within 1 year of the end of the trial.

Table 9-1: Time and events schedule

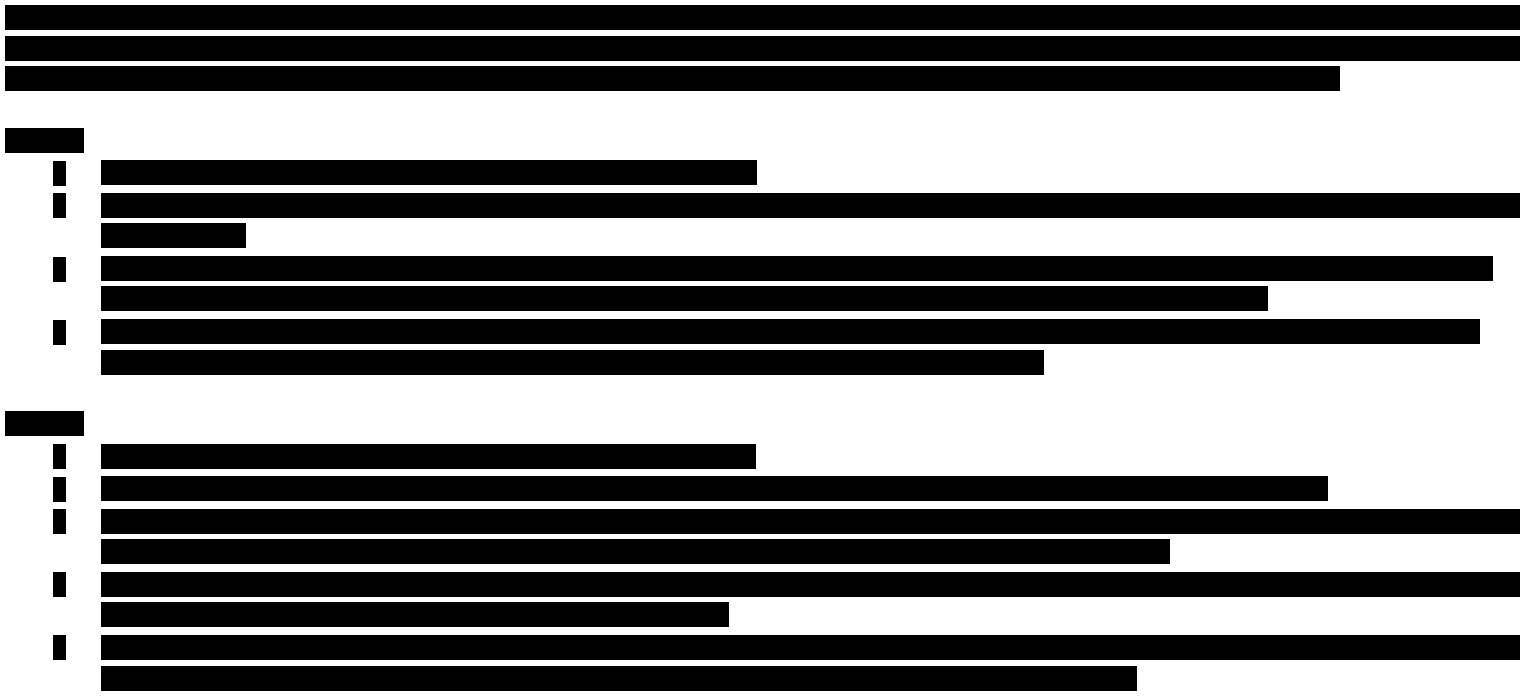
Study Phase ➔	Screening [n]	QUARANTINE PHASE																Follow-up (PK-visit) [q]	Follow-up Phase	Early withdrawal visit
		Admission to quarantine		Human Viral Challenge (HVC)			Post HVC Days										Discharge	Clinic visit(s)	Clinic visit	
Study Day ➔	Day -56 to Day -3	Day	Day	Day 0			Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day 28 (± 3 days)	
Procedure ➔		-2	-1	Pre	Viral Inoculation	Post	1	2	3	4	5	6	7	8	9	10	11	12	13 to 18	
Informed consent	X	X[p]																		
Demographics	X																			
Medical history	X																			
Prior medications	X																			
Eligibility criteria (+)	X	X[m]		X																
Challenge Virus inoculation					X															
Randomisation (a)								(X)	(X)	(X)	(X)									
Administration of IMP (EDP-938 or Placebo) (b, o)								(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Complete physical examination	X	X[m]																X		X
Directed physical examination (inc Ear, Nose, Throat, and Chest)			(X)			X	X	X	X	X	X	X	X	X	X	X	X	(X)		(X)	X

Study Phase ➔	Screening [n]	QUARANTINE PHASE																Follow-up (PK-visit) [q]	Follow-up Phase	Early withdrawal visit
		Admission to quarantine		Human Viral Challenge (HVC)			Post HVC Days										Discharge	Clinic visit(s)	Clinic visit	
Study Day ➔	Day -56 to Day -3	Day	Day	Day 0			Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day 28 (± 3 days)	
Procedure ↓		-2	-1	Pre	Viral Inoculation	Post	1	2	3	4	5	6	7	8	9	10	11	12	13 to 18		
Height & weight, BMI (c)	X	X[m]																(X)		(X)	(X)
Vital signs (HR, RR, SBP, DBP, SpO_2	X	X[m]		TDS			TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	X		X	X
Tympanic temperature	X	X[m]		TDS			TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	X		X	X
12-lead ECG (r)	X	X[m]						(X)	(X)	X	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	X	X
Spirometry (e)	X	X[m]		X			X	X	X	X	X	X	X	X	X	X	X	X		X	X
24-hour tissue count & nasal discharge weight (d)				X			X	X	X	X	X	X	X	X	X	X	X	X			
Symptom diary card			X	TDS			TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	X			
Breath alcohol test	X	X[m]																		X	X
Urinalysis (dipstick)	X	X[m]								X							X	X		X	X
Urine drugs of abuse and cotinine screen	X	X[m]																		X	X

Study Phase ➔	Screening [n]	QUARANTINE PHASE																	Follow-up (PK-visit) [q]	Follow-up Phase	Early withdrawal visit
		Admission to quarantine		Human Viral Challenge (HVC)			Post HVC Days											Discharge	Clinic visit(s)	Clinic visit	
Study Day ➔	Day -56 to Day -3	Day	Day	Day 0			Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day 28 (± 3 days)	
Procedure ↓		-2	-1	Pre	Viral Inoculation	Post	1	2	3	4	5	6	7	8	9	10	11	12	13 to 18		
Urine pregnancy test	X			X														X		X	X
Serum FSH- (post-menopausal women) (f)	X																				
Serum β-HCG pregnancy test (all females) (g)		X[m]																			(X)
HIV, Hepatitis A, B, & C	X																				
Biochemistry	X	X[m]								X			X				X	(X)		X	X
Cardiac enzymes	(X)	X[m]								X			X				X				
Thyroid function test	X																				
Haematology (h)	X	X[m]								X			X				X	(X)		X	X
Coagulation	X	(X)[m]																			
Serum humoral immunity (Virus serology) (i)	(X)	X[m]																		X	X
Study Phase ➔	Screening [n]	QUARANTINE PHASE																	Follow-up	Follow-up	

																			(PK-visit)[q]	Phase	Early withdrawal visit
		Admission to quarantine		Human Viral Challenge (HVC)			Post HVC Days											Discharge	Clinic visit(s)	Clinic visit	
Study Day ➔	Day -56 to Day -3	Day	Day	Day 0			Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day 28 (± 3 days)	
Procedure ↓		-2	-1	Pre	Viral Inoculation	Post	1	2	3	4	5	6	7	8	9	10	11	12	13 to 18		
Nasopharyngeal swab- Respiratory pathogen screen (j)	T	X^m																			
Nasopharyngeal swab- Rapid viral antigen test																		X			(X)
Nasal wash- Virology and Pharmacokinetics (k)	T		X					BD	BD	BD	BD	BD	BD	BD	BD	BD	BD	X			X
Plasma Pharmacokinetics (h, I)								(X)	(X)	(X)	(X)	X	X	X	X	X	X	X	X		X
Adverse events	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Health Questionnaire (PHQ-9)	(X)	$(X)^m$																			
Generalised Anxiety Disorder Questionnaire (GAD-7)	(X)	$(X)^m$																			

KEY NOTES FOR TIME AND EVENTS SCHEDULE

X	Once
BD	Twice Daily, 12 hours between assessments (± 1 hour).
TDS	Three Times Daily, at the same time each day (± 1 hour).
T	To determine tolerance of the procedure only (sample will not be tested).
+	Only the applicable Inclusion/Exclusion criteria will be reviewed at each time point.
a	Subjects will be assigned a randomisation number once the decision to dose is confirmed (i.e. RSV RNA positive confirmed by qicPCR).
b	
c	Height will be taken at Screening only.

d	Distribution of paper issues and bags will start on Day -1, with the first collection on Day 0. Thereafter distribution and collection of tissues will occur at 08:00 (± 1 hour). Tissues will be handed out daily and collection will occur until discharge from quarantine.
e	Spirometry will be performed at the same time each day during quarantine (± 1 hour).
f	A serum follicle stimulating hormone (FSH) test will be performed in all post-menopausal women
g	Blood serum pregnancy test (ß-HCG) will be performed in all female subjects
h	Blood will be drawn under non-fasted conditions. Repeat bloods may be drawn under fasted conditions if a lipid profile (cholesterol and triglyceride) or glucose is required (at PI discretion).
i	Virus serology (RSV neutralisation antibody assay) will be performed within 90 days of inoculation to determine eligibility, on entry to Quarantine, and at Day 28 Follow-up Visit
j	Nasopharyngeal swab for respiratory virus screen to assess for the presence of other respiratory viruses.
k	Nasal wash virology/ Pharmacokinetics samples will be collected at the same time each day during quarantine (± 1 hour) and used for RT-qPCR, and may be used for other secondary or exploratory assessments [redacted] Samples collected between Days 2 and 5 (Study Day 5 Morning) will also be used for qicPCR until a positive result is received (to support dosing decisions).
l	Plasma Pharmacokinetics: plasma samples for IMP assay will be collected as outlined in Appendix 7 (PK Blood Sampling Schedule): The allowable time windows for the sampling are as follows: ▪ ± 5 minutes from the scheduled time for time points ≤ 1 hour from dosing; ▪ ± 15 minutes from the scheduled time for time points > 1 hour from dosing, with NOTE below: o 24 hours timepoint: +/- 1 hour window o 30 hours timepoint: +/- 1 hour window o 36 hours timepoint: +/- 1 hour window o 48 hours timepoint: +/- 2 hours window o 60 hours timepoint: +/- 2 hours window o 72 hours timepoint: +/- 2 hours window ▪ There is no time window requirement for the pre-dose sample. The pre-dose sample must be taken prior to dose.

	For Part 1 subjects who start dosing on the afternoon of Day 5 post viral challenge (PM starters), the 72-hour timepoint after Dose 10 would occur on Day 13. Thus, for a subset of subjects, this timepoint could be after discharge. The guidance for the 72-hour PK sample collection is as follow: ▪ For PM starters who start dosing on Day 5 post viral challenge and meet discharge criteria on Day 12, the 72-hour timepoint sample can be omitted. ▪ For PM starters who start dosing on Day 5 post viral challenge and do not meet discharge criteria on Day 12 and are therefore still in the quarantine unit for the 72-hour PK timepoint, this sample should be collected. ▪ The same guidance for 72-hour PK sample collection will apply to Part 2 when the PK Blood sampling for 5 days TWICE a day dosing for Part 1 will be used for Part 2.
m	Can be performed on Study Day -2 or Study Day -1.
n	Historical pre-screening data collected through the hVIVO generic screening process within 56 days (90 days for viral serology) to 3 days prior to quarantine admission may be used for screening procedures and to determine eligibility without the need to repeat the assessment. Historical pre-screening data obtained prior to this window can be re-assessed any time from 56 days to 3 days prior to viral inoculation.
o	[redacted]
p	When historical pre-screening data collected through the hVIVO generic screening process within 56 days to 3 days prior to inoculation (90 days for viral serology) is used for screening procedures, the study specific ICF will be obtained at quarantine admission (Day -2/-1) from each subject before any study specific procedures are performed.
q	Only Subjects who started IMP dosing on the evening of Study Day 5 (up to Day 8 evening) post Viral Challenge for up to 7 days dosing regimen (Part 2) will return for PK sampling on Study Day 13, 14, 15, 16, 17 and 18 (as applicable) in order to obtain the PK sample(s) associated with the final dose of IMP, for the pre-dose, 0.5-hour, 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, 6-hour, 8-hour, 10-hour, 12-hour, 15-hour, 24-hour, 30-hour, 36-hour, 48-hour, 60-hour, and 72-hour post final dose time points as applicable.
r	ECGs will also be recorded: ▪ First IMP dose (Dose 1): pre-dose, 4 and 8 hours after the initial dose ▪ Dose 2 to Dose 6: pre-dose

	▪ Last IMP dose: 24 and 48 hours post last dose All pre-dose ECGs can be obtained up to 2 hours prior to dosing. Post dose ECGs will be obtained ± 30 minutes of the target time.
Notes:	Parenthesis indicates the assessment may be optional, or at the PI/Investigator's discretion, or as required relative to the start of IMP dosing. For all subjects TDS assessments will commence on Day 0, the first assessment will be pre-virus challenge. 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.

10 RANDOMISATION AND BLINDING

10.1 Randomisation

The randomisation schedule will be generated at the beginning of the study on the assumption that subjects will be randomised as below:

- In the first part of the study, subjects will be randomised to receive one of two doses of EDP-938 or placebo according to 1:1:1.

- Following an analysis and emerging data from Part 1, Part 2 of the study will commence in which up to 84 subjects will be assigned to 1 of up to 3 treatment groups of up to 28 subjects each randomised in a 1:1:1 ratio. Up to a maximum of 84 subjects in total will be enrolled in Part 2.

Subjects will be assigned a randomisation number prior to administration of the IMP.

In Part 1 and Part 2 of the study, dosing will be triggered once the decision to dose is established based on confirmation of RSV infection by qicPCR between Study Day 2 and Study Day 5 (Day 5 morning only). If infection is not confirmed by positive qicPCR by Study Day 5 morning, subjects will be randomised on Study Day 5 and will commence IMP dosing in the evening of Study Day 5..

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

The Randomisation schedule and assigned randomisation number in Part 1 of the study will determine whether a subject is randomised into one of three treatment groups to receive EDP-938 at 600mg OD or 500mg LD followed by 300 mg BD or placebo. The Randomisation schedule and assigned randomisation number in Part 2 of the study will determine whether a subject receives either EDP-938 at 400mg LD followed by 200mg BD or 600mg LD followed by 300mg OD, or placebo.

For the purposes of statistical analysis, placebo subjects from Part 1 will be analysed as a single placebo treatment group, as will placebo subjects from Part 2 based on the assumptions that the placebo substance is expected to be completely inert and have no antiviral properties and subsequently no effect on the efficacy endpoints and their analyses.

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

Randomisation numbers will follow a 5-digit format e.g., Part 1 will start with 10001, 10002, etc, and Part 2 will start with 20001, 20002, etc. A copy of the randomisation code list will be sent to the unblinded pharmacist/ designee preparing the IMP, so that EDP-938/placebo can be prepared for each subject as appropriate.

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

10.1.1 Replacements

Subjects that have been inoculated but not dosed will be replaced. Subjects who are withdrawn before they have received all doses of IMP (i.e. subject has received at least one IMP dose) will not be replaced (refer to Section 7.5.3).

If any of the quarantine groups has less than the planned number of subjects, additional subjects may be recruited into later quarantines, or additional quarantines may be conducted in order to maintain the power of the study.

10.2 Blinding

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

Due to the differing treatment regimens being tested, all subjects will be treated BD in order to maintain the blind between treatment groups. Subjects in the active OD dosing group will have their regimen supplemented by the administration of a placebo matched to EDP-938 in order to mimic the BD dosing group, and subjects randomised to the placebo arm will receive placebo matched to EDP-938 twice a day.

Each subject is accommodated in their own individual room within the quarantine without direct contact with any other subject. In this way subjects assigned to different treatment groups will have no awareness of differences in their treatment or treatment administered.

With the exception of the IMP manufacturer's unblinded pharmacist/designee, the statistician preparing the randomisation code list, the unblinded Clinical Research Associate (CRA) and the Quality Assurance (QA) auditors where necessary, the Investigator and all other clinical and non-clinical staff, (including the Study Statistician, data management staff), and the subjects will remain blinded to the treatment allocation until after the database has been locked and approval for study unblinding has been given. The confidentiality of the randomisation code lists and study blinding will be maintained.

10.3 Unblinding

An independent Statistician at [redacted] Biometrics [redacted] will prepare the randomisation schedule, and the IMP Manufacturer's pharmacist/designee at Hammersmith Medicines Research (HMR) will prepare the subject level IMP doses in line with the randomisation schedule.

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

The emergency code break envelopes will contain information stating either ‘This subject was on active drug (and dosage)’ or ‘This subject was on placebo’. Any premature code-breaking will be explained and justified by the Investigator and hVIVO, and the Sponsor must be promptly informed. If possible, the Sponsor should be consulted before the code is broken, but this will only occur if the safety of the subject will not be compromised.

When the code break envelope is opened, the Investigator must note the date, time, reason for unblinding and the details of the investigator and or designated site staff that broke the blind and record this information according to hVIVO SOPs. The Investigator must also immediately notify the Sponsor’s Medical Monitor (SMM) that the code has been broken.

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

The IMP must be discontinued after unblinding, but the subject will be followed up until resolution of any AEs.

11 CHALLENGE VIRUS

The Challenge Virus is RSV-A Memphis 37b. The Challenge Virus inoculum titre (~4 Log10 PFU) used will be one that has supporting evidence of safety.

11.1 Production

The Challenge Virus strain RSV-A Memphis 37b was isolated from an infant who developed respiratory symptoms without fever. A nasal aspirate taken from the infant tested positive for RSV by antigen detection assays. The RSV was isolated from the infant's nasal aspirate and plaque purified to obtain a "single" virus entity. The selected plaque, B, was used in the manufacture of the Challenge Virus stock at Meridian Life Science®, Inc. USA, according to GMP. The Challenge Virus has undergone quality testing performed during manufacture (identity, appearance, sterility, infectivity, and contaminants) according to pre-determined specifications. The Challenge Virus is stored in a secure -80 °C freezer (normal temperature range -60 °C to -90 °C).

This virus has been used in previous hVIVO Virus Challenge studies and is expected to (as it has in the past) produce cold-like symptoms, such as cough, nasal congestion or low-grade fever [6,46]

11.2 Supply and accountability

hVIVO is obliged to establish a system for control of Challenge Virus in accordance with hVIVO SOPs and as detailed in the AP or a separate Note to File (NTF).

The Investigator will maintain accurate records of receipt and condition of all Challenge Virus inoculum stock used for challenge in accordance with hVIVO SOPs, including details and dates of the quantities dispensed and used in the study. Any departures from the protocol-dispensing regimen will be fully documented.

Accountability records must be maintained as per the hVIVO SOPs. All Challenge Virus storage and accountability records will be available for verification by auditors.

11.3 Preparation and administration

Challenge Virus inoculum will be prepared according to the hVIVO AP and administered in accordance with hVIVO's SOPs. Each subject will be allocated a unique vial containing the Challenge Virus and will receive the inoculum intranasally.

The time from the Challenge Virus inoculum thawing to inoculation should be no longer than 2 hours. All administrations will be made by a member of the clinical team and witnessed by a second member of the team. The exact time of inoculation will be recorded in the administration log and the subject's source notes. Accurate records will be kept of when and how much study inoculum is prepared and used. The oversight process will be signed off prior to administration of the Viral Challenge. Any non-compliance or problems with the inoculation will be recorded in the subject's source notes and reported to the PI/Investigator.

Following inoculation, subjects will be closely observed specifically for potential allergic reactions within 30 minutes, and for the following 24 hours. Post inoculation subjects will lie

flat for 10 minutes then sit up with nose pegs on for 20 minutes. Subjects will continue to be monitored throughout the clinical phase of the study.

11.4 Disposal

Disposal of used and unused Challenge Virus inoculum vials will be in accordance with hVIVO's SOPs.

12 INVESTIGATIONAL MEDICINAL PRODUCT

A complete description of EDP-938 is provided in the Investigator Brochure (IB) and the Pharmacy Manual.

12.1 Description

EDP-938 is a novel, orally administered non-fusion replication inhibitor of RSV that is being developed as a potential treatment for RSV infection. EDP-938 drug product is [redacted]

The physicochemical properties of EDP-938 Drug Substance are detailed in Table12-1.

[redacted]

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

A physical description of the Oral [redacted] product is detailed in Table 12-2.

[redacted]

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

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

[redacted]

12.2 Dispensing and accountability

hVIVO will receive individual doses of subject-specific IMP (oral [redacted] following Qualified Person (QP) certification by HMR QP. All IMP supplies will be used only for this protocol and for no other purpose.

Once received at hVIVO, hVIVO will perform stock level accountability and the IMP will be stored as per section 12.4. IMP accountability will be controlled by hVIVO and monitored by the Study Monitor throughout the study and at study close-out.

IMP will be dispensed as per hVIVO standard processes and the requirements detailed in the Pharmacy manual.

The Sponsor will provide the IMP and retain responsibility for maintenance of the associated essential documents in the Sponsor's TMF.

The 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 also 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.

12.3 Packing and labelling

The preparation of oral [redacted] and labelling of the IMP will be performed by the HMR Pharmacy in compliance with GMP regulations , in accordance with Annex 13 of EudraLex volume 4 and the current version of the 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors'[50,52]. Blinding of subject specific doses will be performed by the HMR Pharmacy.

A release document signed by the HMR QP will be kept in the hVIVO TMF to document labelling and dispensing of the IMP to hVIVO. All documents required to perform GMP activities will be supplied as per the Technical Agreement between HMR and Sponsor.

[redacted]

IMP will be labelled in accordance with the pre-prepared randomisation list. The statistician at [redacted] will prepare the randomisation schedule and HMR Pharmacy will prepare the subject level bottles in line with the randomisation schedule. Package labelling will comply with the requirements of Annex 13 of EudraLex volume 4, and will include at least the following information:

- Sponsor's name
- Pharmaceutical dosage form, route of administration, quantity of dosage units
- Batch and/ or code number to identify the contents and packaging operation
- Trial subject randomisation number
- Directions for use
- 'For clinical trial use only'
- Name of the Investigator
- Trial reference code allowing identification of the trial site
- Storage conditions
- Period of use (use-by date, expiry date or re-test date as applicable), in month/year)
- 'Keep out of reach of children'.

Labelling and packing of study medication will be in accordance with current regulatory standards and sample label(s) will be submitted to the MHRA according to submission requirements.[3, 51-53]

12.4 Storage

[redacted]

12.5 Administration

- In Part 1:
    - 5 consecutive days of dosing in three treatment groups:
        - Group 1: Placebo (n=38); subjects in this group will receive placebo dose BD every 12 hours (±1 hour) interval for a total of 10 doses.
        - Group 2: EDP-938 oral [redacted] loading dose group (n=38): subjects in this group will receive 500mg first dose, and at 12 hours (±1 hour) interval receive 300mg second dose, then 300mg doses BD for a total of 10 doses.
        - Group 3: EDP-938 oral [redacted] 600mg dose group (n=38): subjects in this group will receive a daily 600mg dose followed by a placebo dose at 12 hours (±1 hour) interval for a total of 10 doses.
    - IMP dosing to start on confirmation of positive result by qualitative integrated cycler polymerase chain reaction (qicPCR) on nasal wash. Nasal wash for qicPCR will be performed BD on Study Days 2-5 (Study Day 5 morning only), or until a positive result is achieved, whichever is sooner.
      IMP dosing will be initiated 12 hours (± 1hour) post nasal wash confirmation of a positive qicPCR result.
- In Part 2:
    - The planned treatment groups in Part 2 are as follows:

- Placebo dosed BD (every 12 hours (± 1 hour) interval), and with dosing for 5 days,
- A single Loading dose of 400mg (Dose 1), followed by 200mg second dose at 12 hours (± 1-hour interval), then 200mg doses BD. and with dosing for 5 days
- A single Loading Dose of 600mg (Dose 1), followed by a 300mg dose OD (every 24 hours (±1 hour) interval), and with dosing for 5 days.

- In order to maintain the study blind, subjects in the active OD dosing group will have their regimen supplemented by the administration of placebo matched to EDP-938 in order to mimic the BD dosing group.

[redacted]

All subjects will be dosed orally, in the seated position, and under the direct supervision of the Investigator (or delegate), and in accordance with the randomisation schedule.

12.5.1 Fasting Schedule

Blood will be drawn under non-fasted conditions. Repeat bloods may be drawn under fasted conditions if a lipid profile (cholesterol and triglyceride) or glucose is required (at PI discretion).

12.6 Compliance

IMP will be administered by trained clinical site staff responsible for adequate and accurate IMP administration, accounting and management. Dosing will take place in the quarantine unit and will be monitored by hVIVO quarantine staff to ensure compliance.

The exact times of IMP dosing will be recorded in the relevant dispensing/ administration logs and subject's source notes. Any non-compliance or problems with the administration of the IMP will be recorded in the subject's source notes and reported to the Sponsor if appropriate.

12.7 Overdose

In the event of an IMP overdose the Sponsor is responsible for notifying the MHRA and REC of the potential serious breach (see Section 18.4.3) within 7 days of becoming aware of it. The SME/Sponsor will be contacted within 24 hours or before the next scheduled dose time (see the Pharmacy Manual for further procedural details). General supportive measures will be taken to manage any AEs associated with overdose and subjects will be clinically followed up until the AE has resolved (see section 15).

12.8 Disposal

Unless specifically instructed by Sponsor, the Investigator will not destroy any partly used or unused IMP supply.

On written authorisation from the Sponsor, the Investigator will send unused and partly used IMP supplies and any empty containers for destruction to the address provided at the time of authorisation.

Alternatively, the destruction of unused and partly used drug supplies and any empty containers may be facilitated by the Investigator using a partner service, according to local procedures, and a destruction certificate will be provided. Destruction of any material must be witnessed and documented in writing.

13 ASSESSMENTS AND PROCEDURES

All procedures will be performed according to applicable hVIVO SOPs.

The Investigator may perform additional safety procedures in order to evaluate or manage clinical illness and AEs.

The following assessments and procedures will be performed as detailed in **Table 9-1: Time and events schedule**

Results will be recorded in the source documents.

Where applicable, **unless otherwise stated:**

- Normal ranges described in Appendix 3, and local laboratory reference ranges will be filed in the hVIVO TMF.

During the clinical conduct of the study, the Investigator will use Appendix 6 for clinical assessment of change from baseline.

13.1 Medical and medication history

Personal medical and medication histories and family histories will be recorded, including, but not limited to, detailed histories on allergies (e.g. rhinitis, dermatitis, food, aspirin/non-steroidal anti-inflammatory drugs (NSAIDs) and asthma.

Patient Health Questionnaire (PHQ-9) and Generalised Anxiety Disorder Questionnaire (GAD-7), may be administered at screening and/or admission at the Investigator's discretion.

13.2 Demographics

Demographic data will be recorded at the Screening Visit.

13.3 Height, weight, and body mass index

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

BMI will be calculated as: $BMI\ (kg/m2) = \frac{\text{Weight (kg)}}{\text{Height (m)2}}$

13.4 Complete physical examination

A complete physical examination will include but not limited to an evaluation of the following body systems:

- General appearance
- Skin

- Eyes
- Ears
- Nose
- Throat
- Heart
- Lungs
- Abdomen
- Peripheral pulses
- Lymph nodes
- Neurological/ nervous system
- Musculoskeletal
- Head, neck, and thyroid.

13.5 Directed physical examination

Directed physical examinations will be conducted as deemed appropriate by the Investigator and will include examination of the:

- Ear
- Nose
- Throat
- Chest (via stethoscope).

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

Following viral challenge, URT and LRT symptoms (as described above) will be expected and presumed to represent virus infection consequent to viral challenge, 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 Investigator) to be classed as AEs.

Following viral challenge all unexpected (in the opinion of the Investigator) directed physical examination findings will be captured as AEs, along with all other occurrences that meet the criteria for an AE (see section 15).

13.6 Vital signs

Study specific normal ranges are provided in Appendix 3.

Vital signs assessments will be recorded as follows:

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

- BP: systolic BP and diastolic BP will be measured in millimetres of mercury (mmHg); measurements will be made supine. Where possible, the same arm will be used for all measurements.
- Peripheral arterial oxygen saturation (SpO2%) will be assessed using pulse oximetry.

In the event of a subject having 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 reading. The assessment may then be repeated at the PI/Investigator's discretion and in accordance with hVIVO's SOPs.

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 the CTCAE (referenced in Appendix 5).

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.

13.7 Tympanic Temperature

The study specific normal range for tympanic temperature is detailed in Appendix 3. The severity of out of normal range values will be assigned using the CTCAE (Appendix 5) as a guide.

Temperature is related to definitions of illness (Section 4.2) and to symptomatic and specific therapy criteria; therefore temperatures ≥ 37.9 ºC must be confirmed by a repeat measurement not less than 20 minutes and not more than 60 minutes after the first reading.

The first temperature measurement will be used if it is confirmed by the second reading; both readings will be recorded in the source document.

Temperature may be more frequently monitored in quarantine if appropriate.

Following viral challenge, pyrexia will be expected and presumed to represent virus 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 Investigator) to be classed as an AE.

Following viral challenge all unexpected (in the opinion of the Investigator) pyrexia will be captured as an AE, along with all other occurrences that meet the criteria for an AE.

Febrile illness (FI) is defined as (see section 4.2):

Febrile Illness	Any occurrence of temperature ≥ 37.9 ºC (confirmed by a repeat measurement as ≥ 37.9 ºC within 20 to 60 minutes), **Or**

	Temperature change (post inoculation) of ≥ 2 standard deviations (SD) greater than a baseline measure (from all scheduled temperatures taken by any method on Days -2, -1, and Pre-challenge on Day 0).

13.8 ECG

Study specific normal ranges are provided in Appendix 3.

Twelve-lead ECGs will be obtained to evaluate the electrical activity of the heart. ECGs will be read on site by an appropriately qualified Investigator. Wherever possible the same Investigator will review subsequent ECGs from the same subject for the assessment of any change from baseline.

ECGs will be obtained at Screening, at Quarantine Admission (Day -2 or -1), Day 4, Day 7, Day 11 and at Follow-up Visit Day 28. ECGs will also be obtained pre first IMP dose, at 4 hours post and 8 hours post first IMP dose, then pre-dose for all subsequent doses for the next 2 days (ie, up to Dose 6), at 24 hours and 48 hours post last IMP dose. ECGs may be repeated at the discretion of the PI/Investigator.

All pre-dose ECGs can be obtained up to 2 hours prior to dosing. Post dose ECGs will be obtained ± 30 minutes of the target time.

Any changes from screening during the study will be assessed for their clinical significance. Clinically significant changes will be reported as AEs (Section 15). The PI/Investigator will assess non-clinically significant changes to determine whether they should be recorded as described in Section 15.2.

13.9 Spirometry

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

Spirometry should meet the American Thoracic Society (ATS) / European Respiratory Society (ERS) guidelines criteria (as per ATS/ERS guidelines for standardisation of spirometry). For FEV_1, the highest value from 3 technically satisfactory attempts will be considered. The chosen value should not exceed the next one by more than 150 mL or 5%. If the difference is larger, up to 8 measurements will be made if appropriate.

Predicted values will be calculated according to the formula of the European Community for Coal and Steel (ECCS).

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

13.10 hVIVO Symptom Diary Cards

Subjects will report and assess the severity of any challenge virus related signs and symptoms using the hVIVO Symptom Diary Card. This information will be collected using a paper source document.

Following viral challenge all unexpected (in the opinion of the Investigator) post viral challenge symptoms will be captured as AEs, along with all other occurrences that meet the criteria for an AE.

Previous studies with RSV-A Memphis 37b have used a 10-item symptom questionnaire. The 10-item diary card total symptom score will be used for the secondary endpoint analysis [redacted]

The following symptoms in the 10-item symptoms questionnaire will be graded on a scale of 0-3, where Grade 0 is absence, Grade 1 is just noticeable, Grade 2 is bothersome but does not prevent participation in activities, and Grade 3 is bothersome and interferes with activities.

- Runny nose
- Stuffy nose
- Sneezing
- Sore throat
- Earache
- Malaise (Tiredness)
- Cough
- Shortness of breath
- Headache
- Muscle/ joint ache/ stiffness

[redacted]

The Investigator will assess and review challenge virus related symptoms that are recorded on the Quarantine Subject Symptom Dairy Card following each scheduled completion.

13.11 Nasal discharge collection from paper tissues

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

A daily 24-hour collection will take place throughout the quarantine period. Distribution of paper tissues and bags will start on Day -1, with the first collection on Day 0. Thereafter distribution and collection of tissues will occur at 08:00h (± 1 hour). Tissues will be handed out daily and collection will occur until the discharge from quarantine.

In the event of a subject staying in quarantine beyond the planned day of discharge, the 24-hour distribution and collection of tissues and bags will continue until the subject is finally discharged from quarantine.

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

- 24-hour nasal discharge weight (mucous).

The number of paper tissue used for nasal discharge over 24-hour period will also be collected.

13.12 Routine blood analysis

Section 14.2 describes the routine blood tests that will be performed including, but not limited to, haematology, biochemistry and cardiac enzymes. Additional safety assessments (e.g. coagulation) will be conducted at the discretion of the PI/Investigator, as required.

13.13 Challenge Virus serology

A subject must be sero-suitable to take part in the study; i.e. he/she must have no or low pre-existing serum levels of antibodies specific to the Challenge Virus strain. This antibody titre cut-off for serosuitability will be described in the AP / AP NTF.

Serum levels of pre-existing RSV-A Memphis 37b specific antibodies to the Challenge Virus will be determined using a RSV neutralization antibody assay.

13.14 Nasal samples

The following nasal sampling procedures will be performed during the study:

- Nasopharyngeal swab
- Nasal wash

Where any nasal sampling timepoints occur together the order of sampling will typically be (1) Nasopharyngeal swab, followed by (2) Nasal wash

13.14.1 Nasopharyngeal swab

Nasopharyngeal swab samples will be collected for the following assessments:

- Respiratory Pathogen Screen
- Rapid Viral Screen

Tolerance of the procedure will be determined at the Screening Visit.

13.14.1.1 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 that could potentially contraindicate a subject's participation in the study. Nasopharyngeal swabs will be tested using a direct fluorescent antibody assay (DFA). Any additional screening tests will be conducted at the discretion of the PI/Investigator.

Tolerance of the procedure will be determined at the Screening Visit.

13.14.1.2 Rapid Viral Screen

A rapid viral screen e.g. Rapid Viral Antigen Test (RVAT) will be used to determine the presence of RSV in a nasopharyngeal swab sample prior to discharge from the Quarantine Unit on Day 12. Additional screening tests may be conducted at the discretion of the PI/Investigator.

13.14.2 Nasal wash

Nasal wash samples will be collected to evaluate:

- Viral shedding (as described in section 14.4)
    - qicPCR
    - RT-qPCR
    - Cell based infectivity assay (e.g. plaque assay)
    - Replicative Strand PCR
    - Viral resistance monitoring

- PK testing (as described in section 14.4)
    - Potential measurement of EDP-938 and metabolite levels

Tolerance of the procedure will be determined at the Screening Visit.

13.15 Breath alcohol

Breath alcohol samples will be obtained to determine compliance with the study alcohol restrictions. Alcohol and drugs of abuse testing will be conducted during the study and must be negative at all times. Additional samples may be taken at PI's discretion if positive. Results will be recorded in the source documents.

13.16 Adverse events and concomitant medications

The PI/Investigator is responsible for the detection and documentation of events meeting the criteria for AEs or SAEs (Section 15) from the time of completion of written informed consent until completion of the final Follow-up Visit.

Throughout the study, from screening to the final Follow-up Visit, subjects will be asked to report any unusual, undesirable, or unwanted symptoms, worsening of existing conditions or changes in their health and wellbeing. Subjects will be asked to report any problems and a

delegated physician will periodically enquire about the occurrence of AEs and need for concomitant medications.

During quarantine, subjects will be asked about AEs using open-ended questions, for example:

- 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?

AEs will be assessed and recorded as described in Section 15.

Concomitant medications (prescription and OTC drugs and supplements that a study subject has taken alongside the study intervention) will be recorded.

14 LABORATORY ASSESSMENTS

14.1 Blood volume

A maximum volume of 470 mL of blood may be taken from each subject from Screening Visit through to the final study contact. If additional samples are required in excess of this amount, e.g., to monitor abnormalities, these will be collected at the discretion of the Investigator.

14.2 Safety Blood Samples and Assessments

During the study, safety samples will be collected as detailed below. The hVIVO designated laboratory will be responsible for analysing clinical blood safety samples at scheduled times during the study. Further details on the hVIVO designated laboratory processes for shipment, processing, results and reporting are documented in the Safety Blood “Scope of Work” document. Baseline assessments will be defined in the Statistical Analysis Pan (SAP).

Laboratory results will be reviewed by a study physician. The Investigator may request the collection of additional samples if required for safety monitoring.

Deterioration in a laboratory value (compared to baseline) should only be reported as an AE if the deterioration fulfils the criteria for an AE (see section 15). 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.

Baseline laboratory values that are out of range of normal values but within CTCAE Grade 1, with no accompanying relevant clinical signs and symptoms will not be deemed to be AEs.

All clinically significant laboratory abnormalities deemed to be AEs or SAEs will be documented in the source documents.

The severity of the laboratory abnormalities will be determined based on the grading scales in Appendix 5. Grade 3 laboratory abnormalities must be reported to the PI, who will determine whether further reporting is required.

Relationship to the challenge virus will be assessed. Challenge virus associated laboratory abnormalities may be recorded as AEs.

The PI/Investigator will monitor all clinically significant abnormal laboratory results or assessments until they return to normal or baseline values (i.e. resolve), stabilise, or are no longer clinically significant. Where appropriate, (e.g., after a period of monitoring of an abnormal result), clinically significant abnormalities should be reassessed by the PI/ Investigator to determine whether an AE has changed.

Clinically important abnormalities persisting at the end of the study will be monitored at the discretion of the Investigator until they are resolved or are clinically stable.

As a minimum the following analytes will be measured, others may be included as required.

14.2.1 Biochemistry

- Sodium
- Potassium
- Glucose (random)
- Albumin
- Chloride
- Bicarbonate
- Calcium
- Uric acid
- Total protein
- Creatinine
- Total, direct, and indirect bilirubin
- Inorganic phosphate
- Blood urea nitrogen
- C-reactive protein (CRP)
- Gamma glutamyl transferase
- Alkaline phosphatase (ALP)
- Alanine transaminase
- Lactate dehydrogenase
- Aspartate transaminase (AST)
- Urea.

14.2.2 Thyroid function test

- Thyroid Stimulating Hormone (TSH)
- Thyroxine

14.2.3 Haematology

- Platelet Count.
- White blood cell (WBC) count (absolute)
- WBC differential:
- Neutrophils
- Lymphocyte
- Monocytes
- Eosinophils
- Basophils
- Red blood cell (RBC) count
- Reticulocyte count (% and absolute)
- Haemoglobin
- Haematocrit
- Mean corpuscular volume (MCV)
- Mean corpuscular haemoglobin (MCH)
- MCH concentration (MCHC).

14.2.4 Cardiac enzymes

- Creatine kinase (CK)
- CK-MB
- Troponin T

14.2.5 Coagulation

- Prothrombin time (PT)
- Activated Partial Thromboplastin Time (APTT)

14.2.6 Human Immunodeficiency Virus and Hepatitis A, B, and C

Serum will be tested to detect the presence of the following:

- HIV-1 and HIV-2 antibodies.
- Hepatitis A antibodies (HepA IgM).
- Hepatitis B surface antigen (HBsAg).
- Hepatitis C antibodies (HCAb).

14.2.7 Serum follicle stimulating hormone

Serum samples will be tested for serum follicle stimulating hormone (FSH) in post-menopausal women only.

14.2.8 Serum pregnancy test

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

14.3 Urine Samples and Assessments

14.3.1 Urinalysis

Clinical urine safety analysis will be undertaken using commercially available urine test strips that provide an instant result that will be documented in the source data.

Urinalysis will be performed to evaluate the following parameters:

- Colour
- Specific gravity
- Appearance
- pH.

and to detect the presence of:

- Blood
- Glucose

- Leukocytes
- Ketones
- Nitrite
- Protein
- Urobilinogen
- Bilirubin.

If the dipstick yields abnormal results, a urine sample may be sent for microscopy, culture and sensitivity (MCS), at the Investigator's discretion. MCS will include but is not limited to RBC, WBC, epithelial cells, crystals, casts, and bacteria.

Urine safety analysis values will be evaluated by the Investigator for clinical relevance. Those deemed to be clinically significant will be reported as AEs (Section 15.1.1 and 15.2).

14.3.2 Drugs of abuse and cotinine

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

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

14.3.3 Pregnancy

Urine pregnancy tests will be performed at the times detailed in Table 9-1.

The Investigator may request additional safety assessments and/or unscheduled pregnancy tests in order to evaluate or manage clinical illness.

14.4 Virology Assessments

Samples will be collected as detailed in Table 9-1: Time and events schedule. Details of how the samples will be processed, stored and where relevant, how the analysis will be conducted will be documented in the AP.

14.4.1 Serum RSV neutralising antibody

A RSV neutralising antibody assay will be used to measure levels of pre-existing specific antibodies to the Challenge Virus strain in serum collected at Screening to determine subject serosuitability. The same assay will be used to measure antibody titres in serum samples collected on admission to quarantine and at Day 28 Follow-up Visit.

14.4.2 Respiratory Pathogen Screen

At the times outlined in Table 9-1: Time and events schedule, a respiratory pathogen screen will be performed on a nasopharyngeal swab sample to detect the presence of a number of respiratory viruses that could potentially contraindicate a subject's participation in the study. Nasopharyngeal swabs will be tested using a direct fluorescent antibody assay (DFA).

14.4.3 Rapid Viral Screen

A rapid viral screen e.g. Rapid Viral Antigen Test (RVAT) will be used to determine the presence of RSV in a nasopharyngeal swab sample prior to discharge from the Quarantine Unit. Additional screening tests may be conducted at the discretion of the PI/Investigator.

14.4.4 Viral load

RSV viral load will be measured in nasal washes by RT-qPCR and Cell based infectivity assay (e.g. plaque assay).

RT-qPCR and Cell based infectivity assay (e.g. plaque assay) will also be used to determine viral dynamics (e.g. duration, peak, time to peak).

14.4.4.1 Quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR)

A Quantitative Reverse transcription polymerase chain reaction (RT-qPCR) assay will be used to quantify RSV-A Memphis 37b in nasal wash samples.

14.4.4.2 Cell Based Infectivity Assay

A cell based infectivity assay (e.g. Plaque assay) will be used to quantify infectious RSV-A Memphis 37b in nasal wash samples.

14.4.5 Viral shedding for dosing

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

14.4.5.1 Qualitative Integrated Cycler Polymerase Chain Reaction (qicPCR)

A qualitative integrative cycler PCR (qicPCR) assay will be used to demonstrate virus shedding in nasal wash samples to indicate Challenge Virus infection. The qicPCR assay will be used to support dosing decisions.

14.4.6 Replicative Strand PCR

A replicative strand PCR may be used to evaluate viral replication in cells isolated from nasal wash samples.

14.4.7 Viral resistance

Nasal wash samples may be analysed for potential viral resistance monitoring assessment.

Resistance monitoring assessment if performed, will be conducted by population and /or deep sequencing of the RSV gene to monitor for treatment emergent resistance mutations.

14.5 PK Assessments

14.5.1 Blood Plasma Samples

Blood (plasma) samples for the evaluation of PK parameters of EDP-938 will be collected as outlined in Appendix 7 (PK Blood Sampling Schedule).

Blood samples will be transported, processed and stored in accordance with the AP, and analysed using a bioanalytical assay.

14.5.2 Nasal Wash samples

Nasal wash for the evaluation of PK parameters of EDP-938 will be collected in accordance with Table 9-1 and processed and sent to the Sponsor' PK vendor according to the AP.

15 ADVERSE EVENTS AND TOXICITY MANAGEMENT

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 and hVIVO's SOPs, and also 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.

15.1 Definitions

15.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in subjects. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product, or for the purposes of Human Viral Challenge studies, the Challenge Virus.

An AE includes:

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

An AE does not include:

- 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 conditions present or detected prior to start of IMP or Challenge Virus inoculation administration that does not worsen (including screening findings such as abnormal laboratory results).
- Hospitalisation for elective surgery, social and/or convenience admissions provided they are arranged before the start of IMP administration.
- Over-administration of either the challenge virus, IMP 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 viral symptoms on symptom diary cards (see Section 15.3.6).

15.1.2 Adverse Drug Reaction

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

'Response' in this context means that a causal relationship between a medicinal product and an AEis at least a reasonable possibility[32].

All AEs judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs. The expression 'reasonable causal relationship' means to convey in general that there is evidence or argument to suggest a causal relationship.

15.1.3 Unexpected Adverse (Drug) Reaction

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

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

(b) In the case of any other investigational medicinal product, in the Investigator's Brochure relating to the trial in question'[4].

15.1.4 Serious Adverse Event

A SAE is any adverse event that -

(a) results in death,
(b) is life-threatening,
(c) requires hospitalisation or prolongation of existing hospitalisation,
(d) results in persistent or significant disability or incapacity, or
(e) consists of a congenital anomaly or birth defect;[4]
(f) is an important medical event.

The above characteristics/consequences have to be considered at the time of the event, for example:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which, hypothetically, might have caused death if it were more severe[2].

'Important medical events' - some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered as 'serious' in accordance with the above definition.

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious. Important adverse events/reactions that are not immediately life threatening or do not result in death or hospitalisation, but may jeopardise the subject 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.

15.1.5 Suspected Unexpected Serious Adverse Reaction

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

Medical events will be assessed for expectedness by the PI/Investigator against the Summary of Data and Guidance for the Investigator section of the IB, and any available IB addendum. Any changes to the referenced safety information will be deemed as a change to the risk/benefit profile and will require a substantial amendment to be submitted to the MHRA. This amendment must be approved before the changes are implemented in the study.

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

15.2 Recording and reporting

All AEs and SAEs will be collected from the time of written informed consent until study completion/final study contact or until the resolution of the AE. AEs will be fully recorded in the source documents as they are reported, whether spontaneously volunteered by a subject 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 Investigator should assess the subject's eligibility to continue in the study.

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

- Description of events (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 Virus/ study procedures/ concomitant medication/other).

Any clinically significant abnormal laboratory result, vital sign or other measure will be followed until it returns to normal or baseline values, stabilises, or is judged by the Investigator to be no longer clinically significant.

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 or SAE is assessed by the Investigator as not reasonably attributable to the challenge virus, its occurrence must be fully documented in the source notes.

15.3 Assessment

15.3.1 Description

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

15.3.2 Onset and end

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

15.3.3 Seriousness

The PI/Investigator must record whether the AE meets the definition of serious. If the event is serious (Section 15.5), the PI/Investigator must complete an SAE report form.

15.3.4 Intensity and severity

Severity is a measure of intensity (whereas seriousness is defined by the criteria provided in Section 15.4.).

CTCAE (Appendix 5) will be used as a reference to standardise the severity and grading of AEs and anatomical/ pathophysiological terms, and when collecting, reporting and clarifying database queries of AEs and SAEs.

The severity of an AE that does not appear in Appendix 5 should be determined according to the definitions in Tables 15.1.

15.3.5 Adverse Events critical to the safety evaluation

For AEs deemed critical to the safety evaluation, and therefore to be reported to the Sponsor, refer to Section 15.1.5.

15.3.6 Challenge Virus symptoms

The Investigator will assess and review Challenge Virus related symptoms recorded in subjects' hVIVO Symptom Diary Cards. Symptoms greater than Grade 0 will be expected and presumed to represent virus infection consequent to Viral Challenge, 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 Investigator) to be classed as AEs.

Following Viral Challenge all unexpected (in the opinion of the Investigator) symptoms post inoculation will be captured as AEs, along with all other occurrences that meet the criteria for an AE.

15.3.7 Physical Examination

Any clinically significant change in complete physical examination findings during the study will be documented as an AE.

15.3.8 Directed Physical Examination

Following Viral Challenge, upper and lower respiratory symptoms (nasal discharge, otitis, pharyngitis, sinus tenderness, wheeze and crepitation) may be seen and presumed to represent virus infection consequent to Viral Challenge, 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 Investigator) to be classed as AEs.

15.3.9 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.

15.3.10 Temperature

Following Viral Challenge, pyrexia will be expected and presumed to represent virus 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 Investigator) to be classed as an AE.

Following Viral Challenge all unexpected (in the opinion of the Investigator) pyrexia post inoculation will be captured as an AE, along with all other occurrences that meet the criteria for an AE.

15.3.11 Spirometry

A 15% drop in a spirometry value (compared to baseline), confirmed by a repeat on the same day, will be a Grade 1 (mild) AE. The PI/Investigator will use his/her clinical judgement to

assign severity grades above Grade 1, based on evaluation of clinical signs and symptoms. If the repeated value has returned to normal an AE will not be raised.

15.3.12 Laboratory values

Deterioration in a laboratory value (compared to baseline) should only be reported as an AE if the deterioration fulfils the criteria for an AE. 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 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 Investigator. Laboratory abnormalities detected at screening will be considered as part of the medical history and will not be reported as AEs.

Challenge Virus associated laboratory abnormalities (e.g.: elevated ALT, AST or GGT; decreased neutrophils) may be recorded as AEs (at the discretion of the PI/Investigator).

15.3.12.1 C-reactive protein

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

15.4 Classification of Adverse Events

15.4.1 Severity

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

The CTCAE (see Appendix 5) will be used to standardise the severity and grading of AEs and anatomical/ pathophysiological terms.

The Investigator will use the CTCAE as a reference when collecting, reporting and clarifying database queries of AEs, SAEs and ADRs.

The severity of an AE that does not appear in the CTCAE should be determined according to the definitions in Table 15-1.

Table 15-1: 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

It is important to distinguish between serious and severe AEs. An AE of severe intensity needs not necessarily be considered serious. For example, a migraine headache that incapacitates a subject for many hours may be severe, whereas a stroke that results in a limited degree of disability may be considered mild, but should be reported as a SAE.

15.4.2 Frequency

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

- Single
- Intermittent
- Continuous

15.4.3 Relationship

The relationship of an AE to the IMP will be categorised as shown in Table 15-2.

Table 15-2: Classification of Adverse Event relationship

Classification	Definition
Not related	The AE is related to an aetiology other than the IMP (the alternative aetiology must be documented in the subject's medical record).
Unlikely to be related	The AE is unlikely to be related to the IMP and likely to be related to factors other than IMP.
Possibly related	There is an association between the AE and the administration of the IMP, and there is a plausible mechanism for the AE to be related to the IMP, but there may also be alternative aetiology, such as characteristics of the subject'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 judgment based on the Investigator's clinical experience, the association of the AE with the IMP seems likely.

Classification	Definition
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 Virus
- Study procedures
- Concomitant medication
- Other

15.4.4 Action taken

The Investigator should ensure that adequate medical care is provided to subjects for any AEs, including clinically significant laboratory values related to the IMP. In addition, the Investigator will describe whether any treatment was given for the AE.

The Investigator will classify the action taken with regard to the AE. The action taken should be classified according to the following categories and full details provided as appropriate:

- None
- Non-drug therapy given
- Concomitant medication taken
- IMP dose not changed
- IMP dose adjusted
- IMP administration temporarily interrupted
- IMP administration permanently discontinued
- Subject withdrawn
- Subject hospitalised
- Other

15.4.5 Outcome

An AE should be followed until the Investigator has determined and recorded the outcome or an alternative explanation. The outcome should be classified according to the categories shown in Table 15-3.

Table 15-3: 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

Classification	Definition
Ongoing	Either incomplete improvement or no improvement of the AE, such that it remains on-going
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 subject is lost to follow-up).

15.4.6 Follow-up

All AEs and SAEs must be followed-up by the Investigator, or where appropriate, be referred to the subject's GP or other healthcare professional for follow-up until they are:

- Resolved (return to normal or baseline values), or
- Stabilised, or
- Judged by the PI/Investigator to be no longer clinically significant, or
- An alternative explanation has been provided.

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

15.5 Serious Adverse Event reporting

SAEs must be documented and reported as per Regulatory requirements and hVIVO's SOPs.

Prompt notification of SAEs by the Investigator to the Sponsor is essential so that the Sponsor can meet its regulatory and REC reporting obligations for the study. If the 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 the Sponsor's Pharmacovigilance provider, Pharm Research Associates. In addition, the Investigator can contact the SME directly, if required.

Contact details are detailed in Table 15-4.

- Notification to [redacted] by the Investigator should be made:
  - By telephone as soon as possible and within 24 hours of the Investigator being made aware of the event.
  - In a detailed written report within 24 hours of the Investigator becoming aware of the event.

[redacted].

Table 15-4: Contact details for reporting all SAEs

Contact	Details
Name of Sponsor's Medical Monitor	[redacted]
SME SAE telephone number:	[redacted]
Pharmacovigilance ([redacted] reporting email:	[redacted]
Pharmacovigilance ([redacted]) Fax reporting:	[redacted]
SAE e-mail address:	[redacted]

In addition, any AE resulting in permanent study discontinuation for a subject, even if not serious and regardless of expectedness or causality, must be reported by telephone, email or fax to the Sponsor's Pharmacovigilance provider, [redacted] within 7 calendar days of the PI/Investigator or any other site personnel's knowledge of the event.

The SAE form, AE record and relevant concomitant medication record should be faxed/emailed to the Sponsor's Pharmacovigilance provider, [redacted] within 24 hours of the Investigator or any site personnel's knowledge of a SAE. An updated SAE report form should be forwarded to the Sponsor's Pharmacovigilance provider, [redacted] within 24 hours of receipt of the new/updated information as relevant.

Information relating to the subject's subsequent medical progress must be submitted to the Sponsor's Pharmacovigilance provider, [redacted] as available, until the SAE has subsided or, in the case of permanent impairment, until it stabilises and the overall clinical outcome has been ascertained.

The 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/Investigator)
- Autopsy report (as soon as it is available to the PI/Investigator)
- Consultant reports, as available

All SAEs will be included in the Enanta pharmacovigilance database held by [redacted].

The PI/Investigator must report SAEs 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.

15.5.1 Reporting of SUSARs

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 the course of a clinical trial 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 calendar 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.

In accordance with ICH GCP guidelines, the Sponsor will also inform the Investigator of findings that could affect adversely the safety of subjects and/or impact the conduct of the trial.

Annual safety reporting to the national Competent Authority (MHRA) and the Ethics Committee will be in agreement with ICH guideline E2F “Note for guidance on Development Safety Update Reports (DSUR)”.

In addition, any other safety issue which may alter the current benefit–risk assessment of the IMP will be reported by the Sponsor (or delegate) on an expedited basis to Competent Authorities, Ethics Committees and the Investigator.

The detailed procedure of the SAE/SUSAR reporting will be described in a Pharmacovigilance Management Plan that will be finalised before the start of the study to exactly define the different tasks of the Investigator, Enanta (the Sponsor) and [redacted] (acting on behalf of Enanta).

15.5.2 Adverse Drug Reactions to non-IMPs

Any AEs and SAEs which are related to/caused by a concomitant medication or Challenge Agent, should not be classed as ADRs, SARs, or SUSARs (ADRs, SARs, SUSARs relate only to IMP by definition). However, an SAE caused by a non-IMP would need to be reported to the MHRA/REC for the appropriate action to be taken.

15.5.3 Post-study AEs and SAEs

All SAEs that occur during and up to the Follow-up Visit after the last dose of IMP must be reported by the Investigator to the Sponsor’s Pharmacovigilance provider, [redacted] Sciences as soon as possible, in accordance with Regulatory requirements and hVIVO’s SOPs, and at the latest within 24 hours of becoming aware of the event.

SAEs occurring after the subject has completed the clinical trial, and for which a reasonable possibility of a causal relationship to IMP is assessed by the Investigator, should be reported by the Investigator to the Sponsor regardless of the time that has elapsed (post-trial events).

15.5.4 Pregnancy

If a female subject or partner of a male subject becomes pregnant within 90 days after the last dose of IMP, this must be reported by the Investigator to the Sponsor's Pharmacovigilance provider, [redacted] and Study Monitor/SME by telephone as soon as possible, in accordance with hVIVO's SOPs, and at the latest within 24 hours of becoming aware of the event.

Following the telephone notification, the Investigator must fully and accurately complete the appropriate pregnancy reporting form, which must be e-mailed to the SME and the Study Monitor at the latest within 24 hours of becoming aware of the pregnancy.

Subjects will be advised to contact their GP, as appropriate.

Consent for follow-up of the pregnancy and pregnancy outcome will be sought from the pregnant study subject or the pregnant partner of the male study subject as applicable. Consent for follow-up will be documented in accordance with hVIVO SOPs.

Provided that the appropriate consent is in place, information related to the pregnancy will be collected as per hVIVO's SOPs and the Sponsor's requirements. The completed Pregnancy Reporting Form(s) will be sent to the Sponsor's Pharmacovigilance provider, [redacted] for review and assessment, and subsequent reporting as required.

- A complete evaluation will be documented in the source data to permit transfer to the clinical database.
- The emergency code break envelopes will be requested (Section 10.3) to break the blind for the appropriate study subject to ensure that further care can be based on the actual identity of the study treatment that the subject received.
- hVIVO will maintain contact with the subject for a protracted period of time, 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 subject will keep the subject's GP informed.
- All cases of foetal drug exposure via the parent as a study subject will be reported to the Sponsor and the REC.
- Pregnant females will be referred to their GP or to a specialist, as appropriate

Pregnancy of a study subject or subject's partner during or within 3 months of the date of Challenge is not a SAE, but must still be reported to the Sponsor. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs, and may meet the criteria for an SAE, therefore pregnancies occurring during the study must be followed up until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth or congenital abnormality). Please refer to Section 15.5 for details on the SAE reporting procedure. The Investigator will recommend that male subjects whose partners become pregnant from Quarantine discharge through to the Day 28 Follow-up Visit should contact their GP or a specialist as appropriate. Consent for follow-up will be requested from both partners and a complete evaluation will be documented in the source
data.
Subjects who are lost to follow-up will be managed as described in Section 9.6.

16 STATISTICAL METHODS AND PLANNED ANALYSES

[redacted] will perform the statistical analysis for the study. Full details of the planned statistical analysis (including the Part 1 analysis) will be presented in the Statistical Analysis Plan (SAP). Any deviations from the SAP will be documented in the Clinical Study Report (CSR).

Part 1 data analysis will be reported after completion of Part 1, and based on these results, Part 2 of the study will commence. Data Presentations will be the same in both parts of the study, unless otherwise stated. Part 2 placebo subjects will be pooled across the Part 2 treatment cohorts unless there is a clear difference seen in the data of these subjects, in which they will be analysed only against the active treatment group in their treatment cohort.

16.1 Study analysis sets

The following analysis sets are defined for this study:

- The Intent to Treat (ITT) Analysis Set is defined as all randomised subjects receiving Challenge Virus and at least one dose of IMP. The ITT analysis set will be considered a secondary analysis population for efficacy endpoints.
- The Intent to Treat Infected (ITT-I) Analysis Set is defined as all randomised subjects receiving Challenge Virus and at least one dose of IMP, and meeting the criterion for laboratory confirmed RSV infection as per the definition of laboratory confirmed infection for this protocol (see Section 4.2). The ITT-I set will be considered the primary analysis population for efficacy endpoints.
- The Intent to Treat Infected (ITT-A) Analysis Population is defined as all randomised subjects receiving Challenge Virus and at least one dose of IMP, and meeting the criterion for laboratory confirmed RSV infection (as per the definition of laboratory confirmed infection for this protocol (see Section 4.2) using only assessments prior to taking IMP.
- The Intent to Treat Infected (ITT-B) Analysis Population is defined as all randomised subjects not already in the ITT-A Analysis Population, receiving Challenge Virus and at least one dose of IMP, and meeting the criterion for laboratory confirmed RSV infection (as per the definition of laboratory confirmed infection for this protocol (see Section 4.2) using only assessments after IMP.
- The Per Protocol (PP) Analysis Set is defined as all ITT-I Analysis Set subjects who have no major protocol deviations, and who complete the quarantine period up to the final day of quarantine (Study Day 12), and receive all doses of IMP. The PP Analysis Set will be considered a secondary analysis population for efficacy endpoints.
- The Safety Analysis Set is defined as all subjects receiving challenge virus, regardless of whether they have received IMP or not.
- The PK Analysis set is defined as all ITT subjects with at least one post-dose PK result.

The primary analysis will be on the ITT-I Analysis Set. Analysis of the ITT-A, ITT-B and PP Analysis Sets will be secondary. The safety evaluation will be performed on the Safety Analysis Set.

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

16.1.1 Subgroup analysis

A 'Laboratory confirmed infected' subgroup will be identified and certain pre-specified analyses (to be documented in the SAP) will also be performed by using the ITT-I, ITT-A, and ITT-B analysis sets.

16.2 Sample size

[redacted]

The results of Part 1 may be used to inform a sample size reassessment for Part 2 prior to the start of Part 2 enrolment.

16.3 Interim Analysis

No formal interim analysis will be performed. However, an analysis of Part 1 data will be performed prior to starting Part 2 of the study.

16.4 Statistical Analysis Plan

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

Primary and secondary efficacy endpoints will be analysed descriptively. Continuous variables will be summarised using number of observations, mean (and/or geometric mean, where applicable), standard deviation, standard error, median, lower quartile, upper quartile, minimum and maximum values. Categorical variables will be summarised using proportions (counts and percentages). Statistical analyses will be performed using appropriate two-sided hypothesis tests at the 5% significance level. Normally distributed continuous variables will be presented as mean, difference in means and a 95% confidence interval (CI). The t-test will be used to compare means between groups (and/or an appropriate alternative test, if the t-test assumptions are not satisfied). Methods for checking statistical model assumptions will be described in the SAP.

For endpoints that are not normally distributed (such as total symptom scores), the Wilcoxon Rank-Sum test will be used. No adjustment for multiple comparisons are planned, as this is an early stage study.

The detailed SAP will be developed by [redacted] and approved by the Sponsor prior to any lock of the study database. The SAP will give a more detailed description of the report presentations to be produced for Parts 1 and 2 of the study, respectively, expanding on the protocol specified analysis. Any deviation(s) from the original statistical plan should be described and justified in an amendment to the protocol and/or SAP as appropriate and referenced also in the final clinical study report (CSR). The SAP will describe and account for the occurrence of and extent of missing data, and its possible impact on the study analysis. All baseline assessments will be described in the SAP.

[redacted]

16.4.1 Clinical Study Report

The CSR for the study will be written as set out in the roles and responsibilities.

16.4.2 Subject accountability

The number of subjects receiving Challenge Virus, receiving EDP-938 or Placebo, withdrawing from (also split by reason for withdrawal), and completing the study, and the numbers in each analysis set, will be summarised.

16.4.3 Protocol deviations

Subject 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, subjects will be reviewed for their inclusion/exclusion from the analysis sets.

16.4.4 Demographic and baseline characteristics

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

16.5 Primary efficacy analysis

The AUC for RSV-A Memphis 37b viral load measured in nasal washes by RT-qPCR will be summarised and each active treatment group compared to placebo via a t-test or Wilcoxon Rank-Sum test as appropriate. The primary efficacy analysis will be supported by sensitivity analyses and these will be specified in the SAP.

16.6 Secondary efficacy analysis

The following secondary endpoints will be presented by treatment group:

Clinical Symptoms:

- Effect of EDP-938 compared to placebo on RSV symptoms (using the 10- item diary card), with endpoints including:
    - AUC of total symptom score
    - Peak total symptom score over the duration of quarantine
    - Total symptom score
    - Time to peak symptom score after IMP dosing.
    - Time to resolution from peak symptom.
- Total weight of nasal mucus produced (via weighed paper tissues).

Viral Load:

- Additional viral load endpoints calculated separately using data from RT-qPCR of nasal wash comparing placebo and EDP-938 treated including:
    - Peak viral load
    - Time to peak viral load
    - Time to resolution from peak
    - Time to cessation of virus quantifiable post first dosing

16.6.1 Safety analysis

The following safety endpoints will be presented by treatment group:

- AEs
- Physical Examinations
- Vital signs
- 12-lead ECGs
- Spirometry
- Clinical laboratory results (including biochemistry, haematology, coagulation (if required), cardiac enzymes and urine analysis)

16.6.2 Pharmacokinetic analysis

The following pharmacokinetic endpoints will be presented by treatment group:

- Plasma PK parameters of EDP938 (and metabolites) following repeat dose administration in healthy adult subjects inoculated with RSV-A Memphis 37b: C_{max}, T_{max}, $t_{1/2}$, CL/F, λ_z, Vd/F, C12, C24, AUC_{last}, $AUC_{0\text{-}tau}$, or $AUC_{0\text{-}inf}$

Plasma PK (AUC) correlations with viral load AUC (e.g. RT-PCR) and TSS AUC

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

16.7 Exploratory analysis

[redacted]

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

[redacted]

- [redacted]

[redacted]

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

17 STUDY FILES AND CLINICAL SOURCE DOCUMENTATION

17.1 Investigator's Study File

The PI/Investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be managed in accordance with hVIVO's SOPs.

17.2 Clinical source documentation

Subject data will be collected at site using paper source casebooks which will then be data entered into the [redacted] electronic case report form (eCRF) database.

In cases where data are captured as hard copy e.g., ECG reports or spirometry read outs, the hard copy data will become part of the subject's source documentation and will be transcribed into the eCRF by appropriately trained hVIVO staff. The original paper source will be maintained to enable source data verification by the Monitor.

Source data will be checked for accuracy and completion and will undergo quality control (QC) by hVIVO. The Source Data Agreement and Source Data Management Plan (SDMP) will provide details of what data is deemed to be source and any specific information of the handling and transcription processes performed.

Data captured in other electronic formats and not included in the eCRF database (e.g., laboratory results) will be transferred to S-Cubed via secure transfer as outlined in the Data Transfer Agreements (DTA).

17.3 Data Capture

Data Management will be performed by [redacted]. The DM process will be described in the Data Management Plan (DMP). Data will be entered into the S-Cubed eCRF, a fully validated system compliant with the requirements of 21 Code of Federal Regulations (CFR) Part 11[60] for electronic records and electronic signatures.

[redacted] will be responsible for the creation of the eCRF database and associated validations, the ongoing data cleaning (query raising and resolution), data coding, and database lock. The DMP will be created by [redacted] to document the DM process to be followed. S-Cubed will also create the data validation plan to document the validation checks that will be performed to clean the data. The data cleaning will be performed on an ongoing basis throughout the study and include resolving issues/inconsistencies highlighted through programmed validation checks, manual checks, and reconciliation of data transferred from other vendors.

17.4 Data quality assurance and quality control

Measures will be taken to ensure the accuracy and reliability of data and will include:

- Review of protocol procedures with the PI and study-site personnel prior to the study
- Regular monitoring visits by the assigned study Monitor.
- Direct transmission of clinical and safety laboratory data from a central laboratory into the [redacted] database.

The assigned study monitor will review the study data for accuracy and completeness during on-site monitoring visits. Any discrepancies will be resolved with the PI or designee as appropriate. After upload of the data into the study database, data will be verified for accuracy and consistency with the data sources.

17.5 Data coding

AEs and medical histories will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA).

Concomitant medications will be coded using the most current version of the World Health Organization (WHO) Drug Dictionary Enhanced version.

At the time of coding, the latest version will be used for coding and the version number will be documented in the DMP.

17.6 Database lock

The [redacted] database will undergo validation prior to database lock.

Following [redacted] locking of the database the final database will be transferred to the Study Statistician for statistical analysis and reporting.

17.7 Data protection

The study site will comply with the General Data Protection Regulation (EU) 2016/679[53] and the UK Data Protection Act 2018. hVIVO has in place Data Processing Agreements (which comply with the above laws) with all vendors and partners where personal data will be transferred outside the EU, to bridge the differences in the privacy approaches for data protection law in other countries (e.g. the US).

18 STUDY MANAGEMENT AND ETHICAL RESPONSIBILITIES

The study will be sponsored by ENANTA Pharmaceuticals Inc. and managed by hVIVO Services Limited.

18.1 Regulatory and Ethics Opinions and Good Clinical Practice

This study will be conducted in accordance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki 1996[1], the principles of ICH GCP[2], current regulatory requirements as detailed in the Medicines for Human Use (Clinical Trials) Regulations (SI 2004/1031)[4] and all subsequent amendments, the UK Data Protection Act 2018[5], any other applicable laws and guidance, and any Sponsor requirements.

All ethical and legal requirements will be met before the first subject is enrolled in the study.

18.2 Quality Assurance

A quality assurance (QA) programme is in place to provide assurance that the trial/study is performed and data are generated, documented and reported in compliance with applicable regulatory requirements. The QA audit programme includes audits of systems, processes, facilities and documents.

18.3 Quality Control

QC activities are performed throughout hVIVO to verify compliance and accuracy of all trial/study related activities. These are described in hVIVO SOPs and documented in the records.

18.4 Deviations from the Protocol

18.4.1 Protocol Waivers

Protocol waivers are never acceptable as per all EU competent authorities' guidance (including the MHRA). It is not acceptable to include any subject by protocol waiver – i.e., included despite not meeting all inclusion criteria or fulfilling at least one exclusion criteria.

18.4.2 Protocol Deviations

A protocol deviation log will be used to document any unplanned or unintended departures from the study protocol. Protocol deviations should be recorded as soon as possible after they occur, and if major, reported to the Sponsor immediately by the PI/Investigator.

The PI or delegate will maintain a log of protocol deviations on the study.

18.4.3 Serious breach of the protocol or GCP

Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)[4], as amended by SI 2006/1928[38], contains a requirement for the notification of 'serious breaches' of GCP or the trial protocol:

‘29A.
(1) The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of:
(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25,
within 7 days of becoming aware of that breach.

(2) For the purposes of this regulation, a ‘serious breach’ is a breach which is likely to effect to a significant degree:
(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial’.

Any serious breach of the conditions and principles of GCP or the study protocol in connection with the study will be reported to the Sponsor and the REC.

The Sponsor will be responsible for notifying the MHRA within 7 days of becoming aware of any potential serious breach.

Any potential serious breach of the conditions and principles of GCP in connection with the study will be escalated within hVIVO as soon as an individual becomes aware of the potential breach. Rapid escalation will permit the urgent notification to the Sponsor and allow sufficient time for hVIVO to fulfil the reporting timelines for the potential breach, as specified in UK Regulation 29A[4], should reporting be necessary.

18.4.4 Protocol amendments

Neither the PI nor the Sponsor will alter the study protocol without obtaining the written agreement of the other. For all amendments, an evaluation will be made by the PI and the Sponsor as to whether the amendment is ‘substantial’ or ‘non-substantial’.

Non-substantial amendments include for example, minor administrative or typographical changes to the protocol.

Amendments are ‘substantial’ where they are likely to have a significant impact on subject risk or the clinical trial objectives, specifically the:

- Safety or physical or mental integrity of the subjects
- Scientific value of the trial
- Conduct or management of the trial
- Quality or safety of the IMP used in the trial.

Substantial amendments must be reviewed and approved by the MHRA and/or REC prior to their implementation unless subject safety would be otherwise compromised (i.e., Urgent Safety Measures [USMs]). It is the responsibility of the Sponsor to decide whether an amendment is substantial or not, and therefore whether a substantial amendment requires MHRA authorisation, or an ethical opinion, or both.

When a protocol amendment substantially alters the clinical trial design or the potential risks or burden to subjects, the VIS/ICF will also be amended and approved by the REC, and all active subjects will be asked to reconfirm their continued willingness to participate in the trial.

A log of all protocol amendments, together with their designation as substantial or non-substantial, will be maintained to support clinical study reporting.

18.4.5 Urgent Safety Measures

The Sponsor and the Investigator may take appropriate 'urgent safety measures' to protect clinical trial subjects from any immediate hazard to their health and safety.

USM should be taken immediately. There is no need to wait for MHRA approval before implementing USM.

The Sponsor should telephone the Clinical Trial Unit at the MHRA and discuss the issue with a safety scientist immediately. Should further clarification be required the Sponsor will be contacted by a medical assessor.

The Sponsor must notify the MHRA and the REC in writing, of the measures taken and the reason for the measures within 3 days. This notification should include a covering letter detailing the measures taken, the reason for them, an Annex II substantial amendment form and any supporting documentation.

If the PI (and not the Sponsor) has instigated the USM, the Sponsor should be notified immediately so that they can assess and report the USM within the timelines required.

18.4.5.1 Pandemic

For any period during which a disease is pandemic and a serious risk to human health or potentially a serious risk to human health, notice of USMs taken in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety and the circumstances giving rise to those measures, may be given 'as soon as possible' to the MHRA and the REC.

Written notification to the MHRA and the REC should be provided within 3 days in the form of a substantial amendment and should describe the event, the measures taken and justification for the measures taken.

18.5 Discontinuation of the study

The Sponsor reserves the right to temporarily suspend or discontinue the study for any reason at any time. In addition, the study may be stopped at any time if, in the opinion of the PI or SME, the safety data suggest that the medical safety of subjects is being compromised.

If the study is suspended or terminated for safety reason(s), the Sponsor will promptly inform the PI, 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.

These notifications will occur within 15 days of the termination/suspension.

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.

When a clinical trial has completed as per protocol, the competent authority and REC must be notified within 90 days.

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

18.5.1 Stopping Criteria

The PI 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/SUSAR during the study and the procedures that should be performed in each case are presented in Table 18-1.

Table 18-1: Study stopping criteria

Status	Criterion	Procedure
1	A report has been received of one (or more) SUSAR in any one (or more) subject(s).	If such a status occurs at any point during the study, then further administration of IMP will not take place. The PI and the SME will review the data and make decisions on whether it is appropriate to recommence dosing (via a substantial amendment, if indicated) or terminate the study. Subject follow-up should continue until resolution or stabilisation of SUSAR.
2	No SUSAR 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 but which collectively represent a concern for safety.	If such a status occurs at any point during the study then further administration of IMP will not take place. The PI and the SME will review the data and make a decision on whether it is appropriate to recommence dosing (via a substantial amendment, if indicated) or terminate the study. Subject follow-up should continue until resolution or stabilisation of AEs.

Status	Criterion	Procedure
3	Unexpected virus-related SAE or Unexpected virus-related AEs of clinical concern have been reported following Human Viral Challenge. *Expectedness will be assessed by referring to the challenge virus dossier	If such a status occurs at any point during the study then the PI and the SME will review the data and make a decision based on expectedness* of the viral event. If the event is unexpected, further administration of the virus will not take place. The PI and the SME will review the data and make a decision on whether it is appropriate to recommence inoculation (via a substantial amendment, if indicated) or terminate the study. Subject follow-up should continue until resolution or stabilisation of all such AEs/SAEs and final follow-up on Day 28 (± 3).

In any event, subject follow-up should continue until their final follow-up on Day 28 (± 3 days). Subject follow-up for ongoing AEs will continue until resolution or stabilisation of AEs. The exception to this would be suspension of the study for an USM (Section 18.4.5).

18.6 Study records retention and direct access to source documents

Data will be collected, reviewed and managed throughout the study as outlined in Section 17 and hVIVO's SOPs. The PI shall keep a copy of the source data, the hVIVO TMF and source documents, as specified in the Clinical Trial Agreement (CTA), until notified otherwise by the Sponsor.

hVIVO agrees to allow inspections of the study site and all source documentation by clinical research and audit personnel from the Sponsor, external auditors (including those acting on behalf of the sponsor) or representatives of the MHRA or REC, and will allow direct access to source data and documents.

Direct access to the subject's clinical records is necessary to verify and corroborate the data recorded in the process of source data verification.

During the review of records and documents, the anonymity of the subject will be respected with strict adherence to professional standards of confidentiality. All monitoring activities should be performed in accordance with the Clinical Monitoring Plan for the study.

Source documentation management is described in the SDMP. The PI/Investigator site retains and archives the original source data, retaining all documents as listed in Section 8 of the ICH consolidated guideline on GCP (essential documents for the conduct of a clinical trial)[2].

18.6.1 Archiving

Paper and electronic records generated by hVIVO during the study will be archived as agreed in the CTA and in accordance with the applicable regulations and Sponsor requirements.

18.7 Sponsor responsibilities

18.7.1 General

The Sponsor agrees to adhere to the study protocol, and to comply with the principles of ICH GCP[2], the Declaration of Helsinki 2013[1], the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations (SI 2004/1031)[4], and all subsequent amendments, the UK Data Protection Act 2018[5] and any other applicable regional and local regulations.

The Sponsor has a legal responsibility to obtain MHRA approval to perform the study and to report the results of the study in full to the MHRA. A copy of the MHRA approval will be provided to the PI/Investigator before the start of the study.

18.7.2 No-fault compensation and indemnity

The Sponsor will comply with the Association of the British Pharmaceutical Industry (ABPI)[39] Clinical Trial Compensation Guidelines. The Sponsor will compensate subjects injured as a result of participation in the study, in accordance with the ABPI guidelines, for any harm or ill health incurred. The Sponsor has insurance to cover study-related injuries.

The Sponsor will indemnify the PI (as detailed in a separate document). The indemnity will only apply where all study procedures have been carried out according to this protocol.

hVIVO confirms that it holds a corporate medical professional liability insurance policy which insures hVIVO against any liability incurred as a result of the malpractice or negligence of any of its medical staff (including the PI), while acting within the scope of their role; and that this insurance policy satisfies any local insurance requirements.

18.7.3 Monitoring

The Study Monitor will contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel. In accordance with applicable regulations, ICH GCP, and the procedures of the Sponsor, the Study Monitor will also periodically contact the site and conduct on-site visits. The Study Monitor will ensure that all monitoring visits are conducted according to protocol and regulatory requirements.

During contacts with the study site, the Study Monitor's activities will include:

- Checking and assessing the progress of the study
- Reviewing study data collected to date for completeness and accuracy
- Checking the supply, storage, accountability, disposition and records pertaining to IMP
- Conducting source data verification

- Identifying any issues and addressing resolutions.

These activities will be done in order to verify that the:

- Data are authentic, accurate, and complete
- Study documentation is maintained properly
- AEs are reported accurately
- Safety and rights of the subjects are being protected
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The PI/Investigator will allow the Study Monitor direct access to all relevant documents and records, and allocate his/her time and the time of his/her staff to the Study Monitor to discuss findings and any relevant issues.

At study closure, the Study Monitors will conduct all activities as indicated in Section 18.9.

18.7.4 Audits and inspections

At its discretion, the Sponsor may conduct a QA audit of this study. The Sponsor's auditing procedures will be followed in order to comply with GCP guidelines and ensure acceptability of the study data for registration purposes. If such an audit occurs, the PI/Investigator will give the auditor direct access to all relevant documents, and will allocate his/her time and the time of his/her staff to the auditor as may be required to discuss findings and any relevant issues.

In addition, regulatory agencies (e.g., MHRA) may conduct an inspection of the study. If such an inspection occurs, the PI/Investigator will allow the inspector direct access to all source documents and other study documentation for source data check and/or on-site audit inspection. The PI must allocate his/her time and the time of his/her staff to the inspector(s) to discuss findings of any relevant issues.

18.7.5 Reports to the REC and MHRA

The Sponsor will submit an Annual Safety Report (ASR) and an Annual Progress Report to the REC once a year throughout the clinical trial or on request. The Sponsor will submit a Development Safety Update Report (DSUR) to the MHRA, the DSUR will take into account all new available safety information received during the reporting period.

18.8 Investigator responsibilities

18.8.1 Ethical considerations

In accordance with hVIVO SOPs, hVIVO will submit study related documents to the REC for review and approval including but not limited to the protocol, VIS/ICF, IB and any advertisements. Written approval of these documents must be received from the REC before the first subject is enrolled into the study.

The PI/Investigator will notify the REC of any protocol amendments as described in Section 18.4.4. Written approval must be obtained from the REC for all substantial amendments to the protocol, prior to their implementation, except when necessary to eliminate apparent immediate hazard to the subject (Section 18.4.5).

The PI/Investigator should also obtain a written statement of the composition of the REC. Appropriate reports on the progress of the study will be made to the REC and the Sponsor by the PI/Investigator in accordance with local regulatory practices and in agreement with the Sponsor.

IMP can only be supplied to the PI/Investigator after documentation of all ethical and legal requirements for starting the study has been received by the Sponsor.

The REC and MHRA will be informed about the end of the trial within the required timelines:

- In the event of early termination this is 15 days from trial completion and the reason for termination is required.
- In the case of routine termination, this is 90 days from the protocol-defined end of trial.

18.8.2 Laboratory certification and normal values

The PI/Investigator will provide the Sponsor with the name and location of the clinical laboratory(ies) used for laboratory tests, plus a copy of the certification for all laboratory tests included in the protocol, certification number(s), date(s) of certification, and a list(s) of the normal values for all laboratory tests required by the protocol. These documents must be available prior to any subject being treated in the study. Updated versions of these documents must be provided to Sponsor as appropriate.

18.8.3 Delegation of Investigator responsibilities

The PI should ensure that all persons assisting with the study are adequately informed and trained about the protocol, any amendments to the protocol, their study-related duties and functions, and the study medication. The PI should maintain a list of Investigators and other appropriately qualified persons to whom he/she has delegated significant study-related duties.

18.8.4 Informed Consent Process

A properly executed, written, ICF, in compliance with the Declaration of Helsinki, ICH GCP, and other applicable regulations will be obtained from participants who are willing to participate.

Potential subjects will be sent copies of the VIS and ICF at least 24 hours prior to their Screening Visit/Quarantine admission visit (as applicable) and will be encouraged to read them prior to their appointment. Upon arrival at the Screening Visit/Quarantine admission visit (as applicable), the VIS and ICF are explained and discussed in detail by an investigator and the subjects are given the opportunity to ask any questions, and can also take the information sheet away to consider their participation.

All subjects are required to have a good understanding of English and it is the PI's (or designated individual/delegate) responsibility to ensure that the subject understands the information contained in the VIS and ICF. Once the PI (or designated individual/delegate) has confirmed that the subject has understood the study, including the benefits and risks of participation, the subject and the PI (or designated individual/delegate) must sign and date the ICF.

The ICF must be signed and dated by the subject and countersigned by the PI or designated individual (whoever conducted the consent discussion). All subjects will receive a copy of the signed consent form, and VIS. The VIS and ICF will be copied and filed within the subject notes; the original will be held in the hVIVO TMF.

The subjects 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 participation in the study. The communication of this information must be documented.

If the ICF is amended during the study, the PI/Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the REC. The site must use the amended ICF for all new subjects and repeat the consent process with the amended ICF for any on-going subjects, if required.

18.8.5 Information for General Practitioners

Subjects will be required to consent to their GPs being contacted by the hVIVO team. Confirmation of the subject's medical history will be requested from the subject's GP in order for the PI/Investigator to judge the subject's suitability for the study.

18.8.6 Compensation and Expenses

The Sponsor will reimburse subjects for their inconvenience and out-of-pocket expenses, including travelling costs. All proposed payments to subjects will be approved by the REC prior to the start of the study and the amount of payment will be specified in the VIS.

18.8.7 Liability and insurance

Liability and insurance provisions for this study are specified in the CTA.

18.8.8 Investigator's Protocol Agreement

The Investigator's Protocol Agreement at the front of this document must be signed by the PI. The original or a copy must be kept on file by the Sponsor and the PI/Investigator must retain the original or a copy. The completed Protocol Agreement signifies review and acceptance of the protocol by the PI prior to initiation of the study.

18.8.9 Quality assurance

hVIVO must implement and maintain QA and QC systems which may involve auditing the study.

Any contracted individual or group working on the study must implement QC and/or QA systems in their work on the study.

18.9 Study termination

Upon completion of the study, the following activities, when applicable, must be conducted by the Study Monitor in conjunction with the PI/Investigator, as appropriate:

- Review of site study records for completeness and accuracy
- Return of all study data to the Sponsor (excluding source data)
- Data clarifications and/or resolutions
- Accounting, reconciliation, and final disposition of used and unused study medication (EDP-938 or placebo).

In addition, the Sponsor reserves the right to temporarily suspend or prematurely terminate this study for any reason (see Section 18.518.5).

18.10 GCP Compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guidelines, EU Directive 2001/20/EC, and the applicable regulatory requirements.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

Agreement with the final CSR will be documented by the dated signature of the PI, in compliance with Directive 75/318/EC, Directive 2001/83/EC, and ICH E3.

19 DISCLOSURE OF DATA

19.1 Subject confidentiality

In line with EU Directive 95/46/EEC[37], as transposed into the UK Data Protection Act 2018[5], the PI and hVIVO have a legal obligation to protect at all times the confidentiality of subject personal data from the point of capture, through processing, dissemination in line with consent from the subject and to its final disposition.

The PI/Investigator shall provide assurance to subjects that their confidentiality will be maintained during all audits and inspections of the study site and in any documentation by third parties.

hVIVO investigators, study nurses and other hVIVO personnel will record information about the subjects in a computerised database and in an hVIVO medical record. If the subject consents to participate in this study, any of their medical records may be reviewed by hVIVO staff and auditors for the purposes of checking that the study is being carried out correctly.

Subjects' medical records may also be reviewed by representatives from the REC, government agencies and the MHRA; all have the same legal obligation in respect of confidentiality. Subjects will be assigned a unique number prior to enrolment into the study (Section 7.7). Subjects' names will not be supplied to the Sponsor.

Any samples taken for analysis during the study will be labelled using the subject number. Some laboratories in the UK may require up to two or three identifiers for the accurate tracking and processing of samples, such as subject number, and date of birth. Under no circumstances will a laboratory involved in the analysis of samples in this study be given information regarding the identity of subjects, such as their full name.

19.2 Sponsor confidentiality

As detailed in the CTA, information concerning the IMP and any information such as clinical indications for the IMP, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor and are unpublished, are confidential and must remain the sole property of the Sponsor. The PI/Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose, unless prior written permission from the Sponsor is obtained.

19.3 Publication

[redacted]

[redacted]

[redacted]

[redacted]

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21 APPENDICES

Appendix 1: Patient Health Questionnaire (PHQ-9)[40]

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____
=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

Appendix 2: Generalised Anxiety Disorder Questionnaire (GAD-7)[41]

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

(For office coding: Total Score T____ = ____ + ____ + ____)

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

Appendix 3: Normal ranges

hVIVO Normal Ranges Reference Document for Vital Signs/ECGs and Spirometry

Ratified at Data Standards Meeting 18 May 2016

Vital signs	Lower limit	Higher limit	Units
Tympanic temperature (above 37.8 classed as pyrexia)	35.5	37.8	ºC
Oxygen saturation	Normal is ≥ 95		%
Respiratory rate	10	20	breaths per minute
Heart rate	50	100	beats per minute
Systolic BP	90	140	mmHg
Diastolic BP	60	90	mmHg

ECG

ECG Parameters	Lower limit	Higher limit	Units
HR	50	100	bpm
QRS	60	109	ms
PR interval	120	200	ms
QT	320	450	ms
QTc	Normal for females is < 450		ms
	Normal for males is < 430		
QTcF	320	450	ms
QTcB	320	450	ms
RR	600	1200	ms

Spirometry

Spirometry parameters	Lower limit	Higher limit	Units
FEV1	**Normal if ≥ 80% of the predicted value**		**litres**
FEV1/FVC	**Normal if ≥70% (≥ 0.7) of the base value**		**litres**

Appendix 4: hVIVO Symptom Diary Card

hVIVO
better treatments, faster

Protocol: ENA-CS-001
Visit

Subject Initials: ____
Subject No.: ____

Symptom Diary Card

Date dd mmm yyyy **Time** hh : mm

Morning ☐ **Afternoon** ☐ **Evening** ☑

[redacted]

Volunteer's Initials _____ Physician Initials _____ DD MMM YYYY (dd mmm yyyy) at HH:MM (hh mm)

Appendix 5: AE and Toxicity Grading Scales

Common Terminology Criteria for Adverse Events (CTCAE); Version 5.0. Published: November 27, 2017 (v50: November 27, 2017). U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute.

Appendix 6: Assessment of Baseline by Investigator for Clinical Conduct

During the clinical conduct of the study, the Investigator will use the below for baseline assessment:

Assessments	Baseline
Written Informed Consent	Not Applicable
Eligibility Criteria	Not Applicable
Height, body weight, BMI)	Screening
Medical History	Not Applicable
Demographics	Not Applicable
Prior Medications	Not Applicable
Challenge Virus Inoculation	Not Applicable
Randomisation	Not Applicable
IMP dosing	Not Applicable
Complete Physical Examination	Nearest to Inoculation
Directed physical examination (inc Ear, Nose, Throat, and Chest)	Nearest to Inoculation
Vital signs (HR, RR, SBP, DBP, SpO_2	Nearest to Inoculation
Tympanic Temperature	Nearest to Inoculation
12-lead ECG	Nearest to Inoculation
Spirometry	Nearest to Inoculation
Symptom diary card	Not Applicable
24-hour tissue count & nasal discharge weight	Not Applicable
Breath alcohol test	Not Applicable
Serum humoral immunity (Virus serology)	Not Applicable
Safety Laboratory (Haematology, Coagulation, Biochemistry, Cardiac Enzymes, Thyroid Function Test)	Nearest to Inoculation
Serum FSH- (post-menopausal women), HIV, Hepatitis A, B, & C,	Screening
Serum β-HCG pregnancy test	Nearest to Inoculation
Urinalysis (dipstick)	Nearest to Inoculation
Urine drugs of abuse and cotinine screen	Nearest to Inoculation
Urine pregnancy test	Nearest to Inoculation
Nasopharyngeal swab- Rapid viral antigen test	Not Applicable
Nasopharyngeal swab- Respiratory pathogen screen	Not Applicable
Nasal wash- Virology and Pharmacokinetics	Not Applicable
Plasma Pharmacokinetics	Not Applicable
Adverse events	Not Applicable
Concomitant medications	Not Applicable

Patient Health Questionnaire (PHQ-9)	Nearest to Inoculation
Generalised Anxiety Disorder Questionnaire (GAD-7)	Nearest to Inoculation

Note: Nearest to inoculation is defined as the nearest assessment pre-inoculation.

Appendix 7: PK Blood Sampling Schedule

Blood (plasma) samples for the evaluation of PK parameters of EDP-938 will be collected at the following time points based on the schedule of dosing.

Based on the dose selection for Part 2 (i.e. a combination of different dosing schedule i.e. OD and BD dosing for 5 days), the PK Blood sampling for 5 days TWICE a day dosing for Part 1 will be used for Part 2.

The allowable time windows for the sampling are as follows:

- ± 5 minutes from the scheduled time for time points ≤ 1 hour from dosing;
- ± 15 minutes from the scheduled time for time points > 1 hour from dosing, with NOTE below:
  - 24 hours timepoints: +/- 1 hour window
  - 30 hours timepoint: +/- 1 hour window
  - 36 hours timepoint: +/- 1 hour window
  - 48 hours timepoint: +/- 2 hours window
  - 60 hours timepoint: +/- 2 hours window
  - 72 hours timepoint: +/- 2 hours window
- There is no time window requirement for the pre-dose sample. The pre-dose sample must be taken prior to dose.

PART 1: PK Blood sampling for 5 days TWICE a day dosing

For AM Starters	Timepoints (hr)
Dose 1 (AM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12
Dose 2 (PM)	
Dose 3 (AM)	Pre-dose
Dose 4 (PM)	
Dose 5 (AM)	Pre-dose
Dose 6 (PM)	
Dose 7 (AM)	Pre-dose
Dose 8 (PM)	
Dose 9 (AM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12
Dose 10 (PM)	0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60, and 72.

For PM Starters	Timepoints (hr)[a]
Dose 1 (PM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12
Dose 2 (AM)	
Dose 3 (PM)	Pre-dose
Dose 4 (AM)	
Dose 5 (PM)	Pre-dose
Dose 6 (AM)	
Dose 7 (PM)	Pre-dose
Dose 8 (AM)	
Dose 9 (PM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12
Dose 10 (AM)	0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60, and 72.

[a] Note: The 72-hour timepoint after Dose 10 could occur on Day 13, which for a subset of subjects, could be after discharge. Thus, PM starters who start dosing on Day 5 post viral challenge and meet discharge criteria on Day 12, the 72-hour timepoint can be omitted. The 72-hour PK timepoint sample should be collected if subjects are still in the quarantine unit.

PART 2: DO NOT USE THESE PK SAMPLING SCHEMES; Based on the dose selection for Part 2 (i.e. a combination of different dosing schedule i.e. OD and BD dosing for 5 days), the PK Blood sampling for 5 days TWICE a day dosing for Part 1 will be used for Part 2.

Table A: PK Blood Sampling for up to 5 days ONCE a day dosing

For AM Starters	Timepoints (hr)
Dose 1 (AM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 15
Dose 2 (AM)	Pre-dose
Dose 3 (AM)	Pre-dose
Dose 4 (AM)	Pre-dose
Dose 5 (AM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60, and 72.

For PM Starters	Timepoints (hr)
Dose 1 (PM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 15
Dose 2 (PM)	Pre-dose
Dose 3 (PM)	Pre-dose
Dose 4 (PM)	Pre-dose
Dose 5 (PM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60, and 72.

Table B: PK Blood sampling for up to 5 days TWICE a day dosing

For AM Starters	Timepoints (hr)
Dose 1 (AM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12
Dose 2 (PM)	
Dose 3 (AM)	Pre-dose
Dose 4 (PM)	
Dose 5 (AM)	Pre-dose

For PM Starters	Timepoints (hr)
Dose 1 (PM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12
Dose 2 (AM)	
Dose 3 (PM)	Pre-dose
Dose 4 (AM)	
Dose 5 (PM)	Pre-dose

Dose 6 (PM)	
Dose 7 (AM)	Pre-dose
Dose 8 (PM)	
Dose 9 (AM)	Pre-dose
Dose 10 (PM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60, and 72.

Dose 6 (AM)	
Dose 7 (PM)	Pre-dose
Dose 8 (AM)	
Dose 9 (PM)	Pre-dose
Dose 10 (AM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60, and 72.

Table C: PK Blood Sampling for up to 7 days ONCE a day dosing

For AM Starters	Timepoints (hr)
Dose 1 (AM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 15
Dose 2 (AM)	Pre-dose
Dose 3 (AM)	Pre-dose
Dose 4 (AM)	Pre-dose
Dose 5 (AM)	Pre-dose
Dose 6 (AM)	Pre-dose
Dose 7 (AM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60, and 72.

For PM Starters	Timepoints (hr)
Dose 1 (PM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 15
Dose 2 (PM)	Pre-dose
Dose 3 (PM)	Pre-dose
Dose 4 (PM)	Pre-dose
Dose 5 (PM)	Pre-dose
Dose 6 (PM)	Pre-dose
Dose 7 (PM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 36, 48, 60, and 72.

Table D: PK Blood sampling for up to 7 days TWICE a day dosing

For AM Starters	Timepoints (hr)
Dose 1 (AM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12
Dose 2 (PM)	
Dose 3 (AM)	Pre-dose
Dose 4 (PM)	
Dose 5 (AM)	Pre-dose
Dose 6 (PM)	
Dose 7 (AM)	Pre-dose
Dose 8 (PM)	
Dose 9 (AM)	Pre-dose
Dose 10 (PM)	
Dose 11 (AM)	Pre-dose
Dose 12 (PM)	
Dose 13 (AM)	Pre-dose
Dose 14 (PM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 36, 48, 60, and 72.

For PM Starters	Timepoints (hr)
Dose 1 (PM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12
Dose 2 (AM)	
Dose 3 (PM)	Pre-dose
Dose 4 (AM)	
Dose 5 (PM)	Pre-dose
Dose 6 (AM)	
Dose 7 (PM)	Pre-dose
Dose 8 (AM)	
Dose 9 (PM)	Pre-dose
Dose 10 (AM)	
Dose 11 (PM)	Pre-dose
Dose 12 (AM)	
Dose 13 (PM)	Pre-dose
Dose 14 (AM)	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 36, 48, 60, and 72.