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: 01 NOV 2019

[redacted]

STATISTICAL ANALYSIS PLAN

VERSION 02.00, 01 NOV 2019

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

ENA-CS-001

(Sponsor Protocol Number: EDP 938-101)

Prepared by: [redacted]

For: hVIVO Services Limited (hVIVO)

Sponsor: ENANTA Pharmaceuticals, Inc

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1. STATISTICAL ANALYSIS PLAN APPROVAL FORM

	Signature	Date (ddmmmyyyy)	Time (hh:mm)	Local Time Zone
Author(s): [redacted] Consultant Statistician, [redacted]	[redacted]	06NOV2019	09:02	GMT
Approval(s): [redacted] Project Director, hVIVO Services Ltd (hVIVO)	[redacted]	05NOV2019	13:29	GMT.
[redacted] Executive Director and Head, Biometrics, Enanta Pharmaceuticals, Inc.	[redacted]	01Nov2019		

2. STATISTICAL ANALYSIS PLAN AUTHOR(S)

[redacted]

[redacted]

3. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the curve
BD	Twice daily
BDRM	Blinded data review meeting
β-HCG	Beta human chorionic gonadotropin
BLQ	Below level of quantification
BMI	Body mass index
Bpm	Beats per minute
C_{max}	Maximum (peak) observed concentration
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
%CV	Coefficient of variation, expressed as a percentage
DBP	Diastolic blood pressure
DPE	Direct Physical Examination
ECG	Electrocardiogram
FEV_1	Forced expiratory volume in 1 second
FI	Febrile Illness
FSH	Follicle stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
%GCV	Geometric coefficient of variation, expressed as a percentage
GGT	Gamma glutamyl transferase
HR	Heart Rate
hVIVO	hVIVO Services Limited
HVC	Human Viral Challenge
IMP	Investigational medicinal product
ITT	Intention-to-treat
ITT-I	Intention-to-treat infected
ITT-A	Intention-to-treat infected pre-dose
ITT-B	Intention-to-treat infected post-dose
LDH	Lactate dehydrogenase
LRT	Lower Respiratory Tract
LRTI	Lower Respiratory Tract Illness
LS	Least squares
LSLV	Last Subject Last Visit
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NDA	No detectable antibody
OD	Once daily
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PFU	Plaque forming units
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per protocol

PT	Prothrombin time
Q1	Lower Quartile
Q3	Upper Quartile
qicPCR	Qualitative integrated cycler polymerase chain reaction
RR	Respiratory rate
RT-qPCR	Quantitative reverse transcriptase polymerase chain reaction
RBC	Red blood cell
RNA	Ribonucleic acid
RSV	Respiratory Syncytial Virus
RVAT	Rapid Viral Antigen Test
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard Deviation
SE	Standard Error
SI	Systemic Illness
SOC	System Organ Class
SpO_2	Peripheral arterial oxygen saturation
$T_{1/2}$	Terminal plasma half-life
TDL	TDL Pathology (vendor for safety laboratory assessments)
TEAE	Treatment emergent adverse event
TFL	Tables, Figures and Listings
T_{max}	Observed timepoint of Cmax
TSS	Total symptom score
URT	Upper Respiratory Tract
URTI	Upper Respiratory Tract Illness
WBC	White blood cell
WHO	World Health Organisation

4. INTRODUCTION

This statistical analysis plan (SAP) explains in detail the statistical analyses that will be performed for the hVIVO ENA-CS-001 (EDP 938-101) study. The analysis is outlined within the final study protocol V1.0, dated 23 July 2018 (and protocol amendment 1 (V2.0), dated 04 September 2018, protocol amendment 2 (V3.0), dated 30 October 2018) and protocol amendment 3 (V4.0), dated 11 July 2019. This SAP was approved on 12 February 2019 (Version 01.00) and amended on 01 November 2019 (Version 02.00) and contains a more technical and detailed description of those analyses outlined in the Protocol. In particular, information is provided on the definitions of the analysis sets, and it also details the list of Tables, Figures and Listings (TFL) that will be produced by S-cubed Biometrics for use and inclusion with the Clinical Study Report (CSR). The SAP has been written and finalised before any unblinding of the study.

This study is designed to have up to 2 Parts. Both Parts, together, will not exceed the number of subjects planned for this study (i.e. up to 198 evaluable subjects). Part 2 commenced after an evaluation by the Sponsor and Investigator of the virology, clinical symptom score, pharmacokinetics (PK), and safety data from Part 1. Part 1 data analysis was reported after completion of Part 1, and based on these results, Part 2 of the study has commenced. Data presentations will be the same in both parts of the study, unless otherwise stated.

SAP Version 01.00 contains the pre-planned analysis for Part 1 of the study, this version was amended after analysis of Part 1 to create Version 02.00, which includes clarifications of the planned analysis prior to the unblinding of Part 2.

Any deviations from the protocol specified analyses, and also deviations from analyses stated within this SAP, will be described within the CSR.

5. STUDY OBJECTIVES

5.1. Primary Objective(s)

The primary objective is to evaluate the antiviral activity of EDP-938 compared to placebo in healthy adult subjects inoculated with RSV (Respiratory Syncytial Virus)-A Memphis 37b.

5.2. Secondary Objective(s)

- 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-qPCR) and total symptom score AUC

5.3. Exploratory Objective(s)

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

6. STUDY DESIGN

6.1. Summary of Study Design

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

The study is divided into 2 parts:

- In Part 1*:*
    - 5 consecutive days of dosing in one of 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.
    - 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:

63 subjects will be randomised equally into 1 of 3 treatment groups as below.

- 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.

The study is divided into three phases as shown in Table 1. The overall study design is depicted in Figure 1: Study Design for Subjects.

The days and times of assessments during the study are detailed in Section 6.3.

Table 1: Summary of study phases and procedures

Study phase	Procedures
Screening phase	Screening and enrolment Baseline measurements
Quarantine and challenge phase	Admission to Quarantine Unit Inoculation with Challenge Virus Randomisation and dosing with EDP-938 or placebo Study procedures and assessments Discharge from quarantine
Follow-up (FUP) phase	Follow-up visit and study termination

The duration of a subject's participation from screening to the last scheduled follow-up visit will be a maximum of approximately three months.

The total duration of the clinical phase of the study, from the start of subject screening to the last subject's last scheduled visit (LSLV), including Part 1 and Part 2, is expected to be approximately 18 months.

Subjects will:

- Attend for a screening visit up to 56 days before the scheduled day of viral challenge
- Be admitted to the Quarantine Unit on Day -2/-1
- Be inoculated with challenge virus on Day 0
- Receive IMP dosing starting on confirmation of positive result by qicPCR or in the evening of Study Day 5 if no positive result obtained by qicPCR
- Be discharged from the Quarantine Unit on Day 12 (if appropriate, subjects may reside in quarantine for a further night or longer before discharge)
- Return to the clinic for a follow-up visit on Day 28 (± 3 days)

Figure 1: Study Design

CLINIC/ SCREENING	**QUARANTINE**				**CLINIC** (Part 2 Only)	**CLINIC/FINAL STUDY CONTACT**
Day -56 to Day -3 Screening*	Day -2/-1 Admission to Quarantine Unit	Day 0 RSV-A Memphis 37b Viral Challenge	Days 1 to 12 Dosing and assessments	Day 12 Discharge from quarantine unit/stage**	FOLLOW UP Study Day 13 to 18 Subjects who start dosing on the evening of Study Day 5 (up to Day 8 evening) will return for a PK sample on Study Day 13 to Day 18, as applicable.	FOLLOW UP Study Day 28 (± 3 days)

* 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.

6.2. Randomisation and Blinding

In Part 1 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.

Following an analysis and emerging data from Part 1, Part 2 of the study started in which up to 84 subjects will be assigned to 1 of 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.

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 will be used to assign the subject to one of the three treatment arms in Part 1 of the study (EDP-938 at 600mg OD or 500mg LD followed by 300 mg BD or placebo). A randomization number will be used to link the subjects place in the randomization schedule to their identity in the EDC system. The randomisation schedule and assigned randomisation number in Part 2 of the study will determine whether a subject receives 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.

6.3. Time and Events Schedule

Details of the timing of study assessments and procedures can be found in Table 2 below. Where appropriate, additional safety procedures may be performed at the Study Physician's discretion.

Table 2: 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	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	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	Follow-up Phase	Early withdrawal visit

																			(PK-visit)^{q}		
		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		
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, l)								(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	Subjects will be randomised to a dose group after RSV infection has been confirmed by qicPCR. qicPCR will be conducted on study Day 2 AM through to Day 5 (Study Day 5 morning only), or until a positive result is achieved, whichever is sooner. For subjects who still have no positive result obtained by qicPCR, dosing will then start in the evening of Study Day 5. Part 1: • 5 consecutive days of dosing in three treatment groups: o 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. o Group 2: EDP-938 oral [redacted] loading dose group (n=38): subjects in this 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. Part 2: • 5 consecutive days of dosing in three treatment groups: 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) and at 12 hours (± 1 hour) interval receive a 200mg second dose, then 200mg doses BD every 12 hours (± 1-hour interval) 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.
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.
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.

6.4. Interim Analysis / Data Monitoring

No interim analysis of the data will be performed, as the results from Part 1 are not to be combined with Part 2. However, as specified in the protocol, an analysis of Part 1 data will be performed prior to starting Part 2 of the study, as described below:

Part 1 data analysis will be reported after completion of Part 1, and based on these results, Part 2 of the study will commence. The Part 1 data analysis will produce the full set of data presentations for all Part 1 endpoints as presented in this SAP. This SAP will be finalised before any unblinding of Part 1 of the study.

Part 2 will commence after an evaluation by the Sponsor and Investigator of the virology, clinical symptom score, PK, and safety data from Part 1. The Sponsor will review the emerging data to confirm dose(s) and dose frequencies to be evaluated in Part 2.

7. STUDY ENDPOINTS

Note: This section is based on the Study Objective and Endpoints Section (Section 6) of the protocol. For further detail on specific endpoint definitions and/or methods of analysis please refer to SAP Section 10.

In order to look at the antiviral effect of EDP-938, all efficacy endpoints will use the measurement collected at the time of the first dose of IMP as the starting point in their derivations. For viral load endpoints this will be the last measurement collected prior to first dose of IMP, but for symptoms and temperature this will be from the assessment at the time of the first dose of IMP (which can be prior to or after dosing, depending on whether the subject is dosed in the morning or evening).

7.1. Primary Endpoint

The primary endpoint is the Area Under the Curve (AUC) of RSV viral load measured in nasal washes by quantitative reverse transcription polymerase chain reaction (RT-qPCR), in subjects inoculated with RSV-A Memphis 37b.

7.2. Secondary Endpoints

7.2.1. Efficacy

The secondary efficacy endpoints include, but are not limited to:

- 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 EDP-938 and placebo including:
        - Peak viral load
        - Time to peak viral load
        - Time to resolution from peak
        - Time to cessation of virus quantifiable post first dosing

7.2.2. 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

7.2.3. Pharmacokinetics

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

- Plasma PK parameters of EDP-938 (and metabolites, i.e. EP-024636, EP-024594, and EP-024595) following repeat dose administration in healthy adult subjects inoculated with RSV-A Memphis 37b: C_{max}, T_{max}, $t_{1/2}$, CL/F (parent only), λ_z, Vd/F (parent only), C12, C24, AUC_{last}, AUC_{0-tau}, or AUC_{0-inf}.

  Note: The details of the PK calculations and non-compartmental analysis will be provided in a separate PK Analysis Plan (which is shown in Appendix 15.2).

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

7.3. Exploratory Endpoints

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8. SAMPLE SIZE

The protocol specified (Section 16.2) sample size details are as follows:

[redacted]

[redacted]

[redacted]

Note: The results for Part 1 showed that the sample size assumptions above were a reasonable and/or a conservative approximation, hence for Part 2, two active treatment arms and one placebo group were selected, and described above, each group will include 21 subjects (63 subjects in total).

9. STUDY ANALYSIS SETS

Analysis sets defined below will be reviewed against the study database at a blinded data review meeting (BDRM). The database at this time will be nearly final (i.e. the meeting may result in further data queries/changes post meeting), so inclusion/exclusion of subjects from analysis sets defined at this meeting will be further checked (post meeting) against a final locked database, and will then be finalised prior to unblinding each study Part.

For all analysis sets, subjects who receive a different treatment (EDP-938 or placebo) to the one they were randomised to, will be presented against the treatment they actually received.

The following analysis sets should be taken in combination with the relevant pre-defined subgroups stated in Section 10.1.6, as collectively they show all populations and subgroups to be used in the analyses described in this SAP.

9.1. Intent to Treat (ITT) Analysis Set

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.

9.2. Intent to Treat Infected (ITT-I) Analysis Set

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 (see below for definition of laboratory confirmed RSV infection). The ITT-I analysis set will be considered the primary analysis population for efficacy endpoints.

As per Section 4.2 in the protocol, a laboratory-confirmed RSV infection is defined as the presence of viral shedding, measured in nasal wash. Subjects with incomplete data and no recorded data meeting the definition of this endpoint will be treated as not having met the endpoint.

A subject will fulfil the criteria for viral shedding if:

- At least two positive detections by viral load RT-qPCR assay specific for the challenge virus, reported within two consecutive study days

  and/or

- 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 infectivity assay appropriate for detecting the challenge virus.

For RT-qPCR and the cell based infectivity assay a positive detection is any positive numeric or “detected” value.

Note: ’Not Detected’ log10 copies/mL titre values as reported from RT-qPCR analysis correspond to ‘No’ for the reporting of occurrence of viral shedding.

9.3. Intent to Treat Infected Pre-Dose (ITT-A) Analysis Set

The Intent to Treat Infected (ITT-A) 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 (see Section 9.2 for definition of laboratory confirmed RSV infection) using only assessments prior to taking IMP. The ITT-A analysis set will be considered a secondary analysis population for efficacy endpoints. ITT-A will be a subset of ITT-I.

Note: The assessments prior to dosing with IMP will include all RT-qPCR assessments performed before dosing, including the assessment immediately prior to dosing. In addition, if the infection is seen (via a positive RT-qPCR value) prior to first dose of IMP but the confirmatory value (as per the first part of the viral shedding definition in Section 4.2 of the protocol) is taken after IMP, then that the subject is declared as infected prior to IMP, and hence will fall into the ITT-A Analysis Set.

9.4. Intent to Treat Infected Post-Dose (ITT-B) Analysis Set

The Intent to Treat Infected (ITT-B) Analysis Set 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 (see Section 9.2 for definition of laboratory confirmed RSV infection) using only assessments after IMP. The ITT-B analysis set will be considered a secondary analysis population for efficacy endpoints. ITT-B will be a subset of ITT-I.

Note: The assessments after dosing with IMP will include all RT-qPCR assessments that are after the RT-qPCR assessment that is immediately prior to dosing.

9.5. Per Protocol (PP) Analysis Set

The Per Protocol (PP) Analysis Set is defined as all ITT-I Analysis Set subjects who have no major protocol deviations (as defined in Section 10.3), and who complete the quarantine period up to the final day of Quarantine (Study Day 12) and receive all doses of IMP. Subject exclusions will be determined at a BDRM, which will take place prior to database lock. The PP Analysis Set will be considered a secondary analysis population for efficacy endpoints.

9.6. Safety Analysis Set

The Safety Analysis Set is defined as all subjects receiving Challenge Virus, regardless of whether they have received IMP or not. The baseline and safety analyses will be performed on the Safety Analysis Set.

9.7. PK Analysis Set

The PK Analysis Set is defined as all ITT subjects with at least one post-dose PK result. The PK analyses will be performed on the PK Analysis Set.

10.PLANNED STATISTICAL METHODS

10.1. Statistical Considerations

10.1.1. General definitions

In all applicable summary/analysis presentations of safety endpoints, Baseline is defined as the last non-missing assessment value for a subject, for that particular parameter, that is prior to inoculation of challenge virus unless over-ruled after review of data at the BDRM or otherwise stated in the appropriate endpoint section(s) below, whatever the reason for that assessment (e.g. if it is a repeat assessment, then it should be used as the baseline). For efficacy endpoints, the baseline definition is as per the appropriate endpoint sections below. For the derivation of most efficacy endpoints, the first assessment to be used should be the assessment that was taken at the time of first dose. For example, if a subject was first dosed in the morning of Day 3 then the first RT-qPCR value to be used in the AUC of RT-qPCR viral load (from time of first dose) derivation should be the Day 3 morning assessment.

For subjects that extend their time in quarantine beyond Day 12, the additional assessments beyond Day 12 will be listed only, and will not be used for the derivation of any efficacy endpoints. For the avoidance of doubt, the last scheduled efficacy assessment for those subjects not extending their time in quarantine, will be the Day 12 morning assessment. So, if additional assessments are taken on Day 12, then they will be listed only.

A subject will be considered to have completed the study after his/her attendance at the last planned study visit (Day 28 (± 3 days)), or the last unscheduled visit (if any occur), as applicable.

Within summary presentations/analyses it is envisaged that only scheduled protocol visit values will be used for post-baseline time points. On the clinical database a number of data points have been labelled as unscheduled/additional recordings of data. These data points will be included within subject Listings only. However, at the BDRM the occurrence of such non-scheduled data will be reviewed for each subject to decide if (and how) any such data point(s) should be included within summary presentations/analyses. Any such decisions will be documented in the BDRM minutes.

Where endpoints with assessments on Day 0 (either pre or post challenge) data is to be reported or used in algorithms, the assessments on Day 0 for those endpoints will be compared to the date and time of inoculation to ensure they are pre or post challenge, respectively.

10.1.2. Data Presentation

The full list of TFLs to be produced for the final study analysis are shown in Section 13, and the specific format and content of each data Table/Listing presentation is shown in Section 14.

Summary Tables and Figures will be presented by treatment group (and also for all subjects, for selected data presentations). Parts 1 and 2 will be presented separately. Within all Tables and Figures values for treatment in Part 1 will be labelled as follows:

- “EDP-938 600mg OD”
- “EDP-938 500mg LD/300mg BD”
- “Placebo”

The ordering of treatments shown here represents the order they will appear in Tables.

Within all Tables and Figures, treatment in Part 2 will be labelled as follows:

- "EDP-938 600mg LD/300mg OD"
- "EDP-938 400mg LD/200mg BD"
- "Placebo"

The ordering of treatments shown here represents the order they will appear in Tables.

The scheduled protocol visits will be labelled in (applicable) report presentations as follows:

- Screening
- Day -2 or Day -1 or "Admission", as appropriate
- Day 0

Note: Within some summary Tables only "Baseline" may be shown (as applicable) instead of the above scheduled visits.

- Day x (x=1,…12, as collected, to be included within summary Table)
- Day 28 (FU)
- Withdrawal

Unscheduled visit data will be labelled as "Unscheduled" together with a date in data Listings.

Where duplicate information is collected on both the database and on the vendor data transfer(s) (e.g. sampling date and time) this information will be reconciled by data management and then the information from the vendor data transfer(s) will be included in subject Listings.

All variables will be listed to the same number of decimal places as reported. Descriptive statistics for all endpoints that are continuous data will have the following summary statistics presented in the following order: n, (arithmetic) mean (rounded to one more decimal place than recorded), geometric mean (for pre-specified endpoints only) (rounded to one more decimal place than recorded), standard deviation (rounded to two more decimal places than recorded), %CV (coefficient of variation) (rounded to one decimal place), %GCV (geometric coefficient of variation, for pre-specified endpoints only) (rounded to one decimal place), standard error (for pre-specified endpoints only) (rounded to two more decimal places than recorded), median (rounded to one more decimal place than recorded), lower and upper quartiles (rounded to one more decimal place than recorded), minimum (as recorded), and maximum (as recorded).

Note: for endpoint(s) that require a geometric mean to be produced, and those endpoint(s) can have raw values of 0 (zero), the geometric mean calculation will add an appropriate constant value to all raw values prior to logging and will subtract that constant value from the final calculated anti-logged mean. The constant value used will be documented in the footnote of the tables. An example of such a calculation is shown below:

Geometric Mean = anti-log {mean (logged (base 10) endpoint values + 1)} - 1

Categorical variables will be summarised using proportions (counts and percentages). The specific approach to calculating percentages (relevant denominator) is detailed within each (relevant) Table template (Section 14).

Unless otherwise stated in the appropriate endpoint section(s) below, laboratory/efficacy parameter values that are below the level of quantification (BLQ) will be set to zero in computations for summary presentations and analysis but will be noted as below the limit of quantification in subject Listings.

10.1.3. Statistical Testing and Estimation

Hypothesis testing will be performed for the primary and secondary efficacy endpoints, as specified and described in Sections 10.7.1 and 10.7.2. Analyses will be performed between each EDP-938 treatment group and the placebo group, and also between the two EDP-938 treatment groups.

All statistical analyses will be performed using appropriate two-sided hypothesis tests. P-values will be rounded to 3 decimal places. All p-values that round to 0.000 will be presented as <0.001 and p-values that round to 1.000 will be presented as >0.999.

10.1.4. Handling of Dropouts or Missing Data

In general, missing data will not be imputed and all summary statistics will be reported based upon observed data. For a limited number of summary presentations, missing data rules will be introduced. In particular methods of handling missing data for the efficacy endpoints (Section 10.7), incomplete dates for adverse events (Section 10.8.1) and incomplete dates for concomitant medications (Section 10.5) are presented. For any other data which has partial dates, which are required for use in time related calculations, these dates will be completed using a suitably conservative approach. Dates will be shown in subject Listings as they have been recorded.

10.1.5. Multiple Comparison/Multiplicity

As this is an early phase study, with the main objectives being safety and PK, no adjustments will be made to handle multiplicity.

10.1.6. Examination of Subgroups

It was intended that certain pre-selected endpoints were to be repeated for the subgroup 'Laboratory confirmed infected'. This subgroup is defined as those subjects who are laboratory-confirmed infected (by viral shedding, see Section 9.2). However, the ITT-I, ITT-A and ITT-B analysis sets already incorporate this subgrouping definition, and hence there is no need to subgroup any analysis sets further.

10.1.7. Model checking and sensitivity analyses

No model checking will be performed. For each comparison between treatment group performed using an ANCOVA, the Wilcoxon rank-sum test with two-sided 5% statistical significance, will also be provided.

10.1.8. Software

Data will be reported using SAS (version 9.4 or later).

10.1.9. Data Conversion (CDISC)

For the reporting of this study both CDISC SDTM (SDTM Implementation Guide version 3.2) and ADaM (ADaM Implementation Guide version 1.1) standards will be applied. One set of CDISC data sets will be provided containing data from Part 1 and Part 2.

10.2. Subject Disposition

The subjects inoculated, randomised, receiving at least one dose of IMP, withdrawing (including reason for withdrawal) from and completing the study, and the analysis populations will be summarised by treatment group and across all subjects.

The number of subjects attending each of the following scheduled visits will be listed for all subjects: Screening, Day -2/-1 (or Admission), Day 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 28 (FU) and Withdrawal.

10.3. Protocol Deviations

Subject data will be reviewed for major protocol deviations by a qualified clinical reviewer prior to database lock and unblinding, at the blinded data review meeting (BDRM). Subjects with any major protocol deviations will be documented within the BDRM minutes, and such subjects will be excluded from the PP analysis set.

Protocol deviations will be listed.

10.4. Demographic and other baseline characteristics

The Safety Analysis Set will be used in all presentations of demographic and baseline data. No statistical testing will be used to compare treatments for different baseline characteristics.

10.4.1. Demographics

Demographic variables at screening (sex, age, ethnicity, race, height (cm), weight (kg), and body mass index (BMI) (kg/m^2) [BMI is recorded on the case report form (CRF) and included within the study database, therefore it does not require derivation]), will be summarised by treatment group and across all subjects.

10.4.2. Other Baseline Characteristics

Smoking history and alcohol consumption will be summarised by treatment group and across all subjects for the following items:

- Smoking history status (Never smoked / current smoker / previous smoker)
- Alcohol history status (Never / current / previous)

All substance use history data will also be listed. Recreational drugs of abuse will also be listed.

10.4.3. Medical History

As stated in the protocol, medical history data will be listed. Medical History will be coded using MedDRA, Version 21.1.

10.5. Prior and Concomitant medications

Concomitant medication terms will be coded using the World Health Organisation (WHO) Drug Dictionary Enhanced (WHO Drug Global Version 2018:3, September 1, 2018). Medications will be assigned as being prior to or concomitant with IMP treatment (i.e. given prior to or after receiving IMP treatment) based on the start and stop dates of the medication and the date of receiving IMP treatment.

If the medication stop date is before the date of inoculation, the medication will be assigned as being prior to inoculation. If the medication stop date is before the date of IMP treatment, the medication will be assigned as being prior to IMP treatment. In all other situations, the medication will be assigned as being concomitant with the IMP treatment.

Note: Start and Stop times will not be used for determining if a medication is concomitant or not.

All concomitant medications will be separately summarised, using the Safety Analysis Set, by treatment group (and across all subjects), Drug Class (L2) and generic name. Prior (to inoculation and IMP) medications will be identified in a subject listing. If a subject has separate periods of taking specific medications, then that medication is only counted once within the period of observation (i.e. prior to inoculation, prior to IMP or concomitant) where it is taken.

10.6. Treatment and Inoculation exposure

The number of subjects inoculated and the number of subjects receiving IMP treatment will be summarised (as part of the Subject Disposition data presentations (Section 10.2)).

10.7. Efficacy Analysis

In terms of the efficacy analysis, the primary analysis will be based on the ITT-I analysis set, with secondary analyses populations based on the ITT-A, ITT-B, ITT and PP analysis sets. Only the primary and main secondary efficacy endpoints, as stated in Sections 7.1 and 7.2.1, will be presented on all of these analysis sets if they contain different subjects. All efficacy endpoints that relate to symptom scores will be based on the 10-item symptom diary card [redacted]

10.7.1. Primary Efficacy Analysis

The primary endpoint is the AUC of RSV-A Memphis 37b viral load measured in nasal washes by RT-qPCR, from the measurement collected at the time of the first dose of IMP until the last measurement collected up to Day 12 (Quarantine discharge). The viral load data will be supplied as log10 copies/mL and will be used for this primary efficacy analysis and to calculate the AUC using the trapezoid rule [1]. AUC will be compared between each dose level of EDP-938 and placebo, separately, and also between the two active dose levels of EDP-938, by means of a full set of descriptive statistics and an ANCOVA with treatment group as a main effect and the baseline value as a covariate. The baseline value will be the RT-qPCR viral load value from the last measurement collected prior to the first dose of IMP. The three treatment comparisons will be presented, including the LS means of the treatment differences for each comparison together with the corresponding two-sided 95% confidence interval and the p-values will be presented. The equivalent Wilcoxon rank-sum tests will also be provided.

The analysis will be performed by the PROC MIXED procedure in SAS using code similar to that below.

```
proc mixed data=XXXXX;
class treatment;
model AUC= baseline treatment / ddfm=kr;
lsmeans treatment / diff cl;
run;
```

As nasal washes are scheduled to be taken twice daily for Days 2 to 11 (and once on Day 12), in order to calculate the AUC, the actual time that the assessment was collected will be used within the AUC calculation. The AUC calculation will be based on the available non-missing assessment values between the start and end of the defined AUC time period. However, for an AUC to be derived, the subject must have at least one non-missing data recording at the start of the AUC period (e.g. date of first dose of IMP) and also at the end of the AUC time period (e.g. Day 12). In addition, the subject must have at least 1 non-missing data recording on each day between the start and end of the defined AUC time period (i.e. at least 1 out of the 2 possible assessments on each Day)). Any missing RT-qPCR data will be reviewed at the BDRM, for its potential impact on this endpoint, and any decisions to include subjects that fail these criteria above will be documented in the BDRM minutes.

Note: For the reporting of AUC, where appropriate, RT-qPCR values that are 'Not Detected' or are at or below the limit of quantification will be re-assigned using the substitution values shown in the table in Appendix 15.1.

As an additional sensitivity analysis, the AUC of RSV viral load measured in nasal washes by RT-qPCR will be presented for a fixed time period, from the measurement collected at the time of the first dose of IMP to the scheduled assessment occurring 6.5 days afterwards (e.g. if a subject does not have a positive qicPCR then they will be dosed on Day 5 (evening) and they will be followed up until Day 12 (morning) 14 assessments in total) – which represents the longest possible AUC time period where all subjects are followed for the same fixed period of time.

A second sensitivity analysis of AUC of RSV viral load measured in nasal washes by RT-qPCR will be presented for a fixed time period, which will include data from the morning assessment on Day 2 (i.e. the first RT-qPCR assessment measured) through to Day 12.

A third sensitivity analysis of AUC of RSV viral load measured in nasal washes by RT-qPCR, from the measurement collected at the time of the first dose of IMP until the last measurement collected up to Day 12 (Quarantine discharge), will be presented where the AUC will be calculated using a linear scale (unlogged) viral load data (i.e. the supplied value will be anti-logged to get a value as copies/mL).

The AUC analyses will be summarised by treatment group. The same statistical testing methods as applied to the main analysis of the primary endpoint will be applied to each sensitivity analysis. For the third sensitivity analysis, the individual AUC data will be log-transformed (base 10) prior to statistical analysis and the geometric mean and %GCV will be shown.

As well as a descriptive statistics summary of RT-qPCR values, the mean RT-qPCR values (+/- 1 Standard Error (SE)) will be displayed graphically by day (relative to first dose of IMP) and assessment, and treatment group. In order to calculate the time point that each assessment will be presented against, the last RT-qPCR measurement collected prior to the first dose of IMP will be assigned to be the value at time point 1, while measurements collected on subsequent assessments and days will be assigned to subsequent time points in sequential order (i.e. time point 2, 3 and so on). Time point 1 will be presented against Day 0 assessment 1, while subsequent time points will be presented against Day 0 assessment 2, Day 1 assessment 1, and so on.

[Line graph: y-axis = mean of RT-qPCR (log10 copies/mL), x-axis = day relative to dosing, one line for each treatment group on same plot].

Note: For multiple assessments taken within each day, so as to be able to plot mean values across subjects (within a treatment group) by day, the actual collection time point (which may differ across subjects) will not be used. Rather all 1st /2nd assessments will have mean values separately calculated and plotted as two separate means within each day. These two means will be shown equally spaced along the x-axis within the graph.

10.7.2. Secondary Efficacy Analyses

Secondary efficacy analyses will be performed on the following endpoints:

10.7.2.1 AUC of total symptom score

Total symptom scores (from the 10-item symptom diary card) will be used to calculate the AUC, from the assessment at the time of the first dose of IMP (can be prior to or after dosing, depending on whether dosed in the morning or evening), i.e. baseline, until Day 12 (Quarantine discharge), for each subject using the trapezium rule [1].

Symptoms are recorded on the symptom diary cards, assessed 3 times daily for Day 1 to Day 11 (and once for Day 12). The following types of symptoms are recorded (on a grading scale, 0 to 3 (or 0 to 4 for the Shortness of Breath symptom)):

- Upper Respiratory Tract (URT): runny nose, stuffy nose, sore throat, sneezing, earache.
- Lower Respiratory Tract (LRT): cough, shortness of breath.
- Systemic: headache, malaise, muscle/joint ache/stiffness.

A total symptom score will be derived for each subject, separately for each assessment (symptom diary card) on each day (Day 0 to Day 12) as follows:

- For each assessment, sum the 10 observed symptom grade values for each symptom diary card to obtain a total symptom score for each symptom diary card. If the subject does not have all 10 observed values on a specific symptom diary card being considered, then total symptom score will not be calculated for that symptom diary card. It is expected that subjects will not have missing data.
- The AUC calculation will be based on the available non-missing calculated total symptom scores between the start and end of the defined AUC time. However, for an AUC to be derived, the subject must have at least 1 non-missing calculated total symptom scores at the start of the AUC period (e.g. date of first dose of IMP) and also at the end of the AUC time period (e.g. Day 12). In addition, the subject must have at least 2 non-missing data recording on each day between the day after the start, and the day before the end, of the defined AUC time period (i.e. at least 2 out of the 3 possible assessments on each Day)). Any missing total symptom score data will be reviewed at the BDRM, for its potential impact on this endpoint, and any decisions to include subjects that fail these criteria above will be documented in the BDRM minutes.
- As symptoms are scheduled to be taken 3 times daily for Days 0 to 11 (and once on Day 12), in order to calculate the AUC, the actual time that the assessment was collected will be used within the AUC calculation.

As an additional sensitivity analysis, the AUC of total symptom score will be presented for a fixed time period, from the assessment at the time of the first dose of IMP (can be prior to or after dosing, depending on whether dosed in the morning or evening), to the scheduled assessment occurring 6.5 days afterwards.

A second sensitivity analysis of AUC of total symptom score will be presented for a fixed time period, which will include data from the Day 0 (Pre-Challenge) assessment through to Day 12.

The AUC of the total symptom score will be summarised by treatment group and modelled in the same way as the main analysis of the primary endpoint.

The total symptom scores will be summarised (including a geometric mean) by timepoint (i.e. day relative to first dose of IMP and assessment) and treatment group, and symptom scores from the symptom diary card will be listed.

As well as a descriptive statistics summary of total symptom score values, the mean total symptom score values (+/- 1 Standard Error (SE)) will be displayed graphically by day (relative to first dose of IMP) and assessment, and treatment group. In order to calculate the time point that each assessment will be presented against, the last total symptom score measurement collected at the time of the first dose of IMP will be assigned to be the value at time point 1, while measurements collected on subsequent assessments and days will be assigned to subsequent time points in sequential order (i.e. time point 2, 3 and so on). Time point 1 will be presented against Day 0 assessment 1, while subsequent time points will be presented against Day 0 assessment 2, Day 0 assessment 3, Day 1 assessment 1, and so on.

[Line graph: y-axis = mean of total symptoms score, x-axis = day relative to dosing, one line for each treatment group on same plot].

Note: For multiple assessments taken within each day, so as to be able to plot mean values across subjects (within a treatment group) by day, the actual collection time point (which may differ across subjects) will not be used. Rather all 1st /2nd /3rd assessments will have mean values separately calculated and plotted as three separate means within each day. These three means will be shown equally spaced along the x-axis within the graph.

10.7.2.2 Peak total symptom score over the duration of quarantine

Using the scheduled protocol assessments from the assessment at the time of the first dose of IMP (can be prior to or after dosing, depending on whether dosed in the morning or evening) to Day 12 (Quarantine discharge), this endpoint corresponds to the highest total symptom score (defined as the sum of all 10 individual composite symptoms). Subjects who had no symptoms will be given a peak of 0.

The peak symptom score will be summarised by treatment group and modelled in the same way as the main analysis of the primary endpoint.

10.7.2.3 Time to peak symptom after IMP dosing

This endpoint corresponds to the time (days) from the assessment at the time of the first dose of IMP (can be prior to or after dosing, depending on whether dosed in the morning or evening) until the peak (as defined in Section 10.7.2.2) is observed. If the peak occurs on more than one day then the first occurrence is selected. Subjects who stay symptom free during quarantine will have their peak assigned to the time of their last assessment.

The time to peak symptom will be summarised by treatment group and modelled in the same way as the main analysis of the primary endpoint.

10.7.2.4 Time to resolution from peak symptom

This endpoint corresponds to the time (days) to resolution of symptoms, which is from time of peak symptom until the start of the first 24 hour symptom-free period after the peak. Note: the 24 hour symptom-free period has to be a minimum of 24 hours (as measured by the exact assessment dates and times) and no symptoms must have occurred during that time period. Subjects who did not have a 24 hour symptom-free period after their peak will be assigned to the time of their last assessment. Subjects who had no symptoms will be excluded from this analysis.

The Time to resolution will be summarised by treatment group and modelled in the same way as the main analysis of the primary endpoint.

10.7.2.5 Total weight of nasal mucus produced

Total weight of nasal discharge (grams) will be calculated as the sum of mucus weights taken from the assessment at the time of the first dose of IMP (can be prior to or after dosing, depending on whether dosed in the morning or evening) to Day 12 (Quarantine discharge). Total mucus weight will be summarised by treatment group. The same statistical testing methods as applied to the main analysis of the primary endpoint will be applied.

As well as a descriptive statistics summary of total weight of nasal discharge, the mean weight of nasal discharge values (+/- 1 Standard Error (SE)) will be displayed graphically by day (relative to first dose of IMP) and assessment, and treatment group. In order to calculate the time point that each assessment will be presented against, the last weight of nasal discharge measurement collected prior to the first dose of IMP will be assigned to be the value at time point 1, while measurements collected on subsequent days will be assigned to subsequent time points in sequential order (i.e. time point 2, 3 and so on). Time point 1 will be presented against Day 0, while subsequent time points will be presented against Day 1, Day 2, and so on. Also, given that weight of nasal discharge values span a 24 hour period, the point used for each timepoint will be set midway between each day that forms the boundary of each 24 hour time period.

[Line graph: y-axis = mean weight of nasal discharge, x-axis = day relative to dosing, one line for each treatment group on same plot].

10.7.2.6 Peak viral load measured in nasal washes by RT-qPCR

Using the scheduled protocol assessments from the last measurement collected prior to the first dose of IMP to Day 12 (Quarantine discharge), this endpoint corresponds to the highest observed RT-qPCR viral load value for each subject. Subjects who stay undetectable (i.e. a 'Not Detected' value) during quarantine will be given a peak equivalent to an undetectable value (as shown in Appendix 15.1).

The peak will be summarised by treatment group and modelled in the same way as the main analysis of the primary endpoint.

10.7.2.7 Time to peak viral load measured in nasal washes by RT-qPCR

This endpoint corresponds to the time (days) from the last measurement collected prior to the first dose of IMP until the peak is observed. If peak is seen on more than one day, then take first occurrence. Subjects who stay undetectable during quarantine will have their peak assigned to the time of their last assessment.

The time to peak will be summarised by treatment group and modelled in the same way as the main analysis of the primary endpoint.

10.7.2.8 Time to resolution from peak viral load measured in nasal washes by RT-qPCR

This endpoint corresponds to the time (days) from when the peak value was observed until the first confirmed undetectable assessment timepoint (after which no further virus is detected) after the peak viral load. Subjects who did not have a confirmed undetectable after their peak will be assigned to the time of their last detectable assessment. Subjects who stay undetectable during quarantine will be excluded from this analysis.

The time to resolution will be summarised by treatment group and modelled in the same way as the main analysis of the primary endpoint.

10.7.2.9 Time to cessation of virus detection post first dosing measured in nasal washes by RT-qPCR

This endpoint corresponds to the time (days) from the last measurement collected prior to the first dose of IMP until the first confirmed undetectable assessment timepoint (after which no further virus is detected) after the peak viral load measured in nasal washes by RT-qPCR. Subjects who did not have a confirmed undetectable assessment after their peak are censored at their last detectable assessment. Subjects who stay undetectable during quarantine will be excluded from this analysis.

The time to cessation will be summarised by treatment group.

Kaplan-Meier plots [2] will be displayed by treatment group showing the time to cessation of virus detection (with the time axis as days since peak). A table will accompany the plot and will display the Kaplan-Meier estimates of the cumulative proportion of subjects' event free at specific time points by treatment group. In addition, the lower quartile, median and upper quartile of the survival times in each treatment group will be presented. A log rank test will be performed to compare the survival times between each dose level of EDP-938 and placebo, and also between the two active dose levels of EDP-938, and the corresponding p-values will be presented.

10.7.3. Exploratory Efficacy Analysis

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10.8 Safety Analysis

All analyses of safety endpoints will be descriptive. The safety analysis set will be used for all safety presentations. No statistical analysis of safety data will be performed.

10.8.1. Adverse Events

The incidence of treatment-emergent AEs (TEAE), both overall and by severity, seriousness and causality, will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), preferred term and treatment group.

All adverse events will be coded using MedDRA, Version 21.1.

An adverse event will be classified as treatment emergent if the onset date/time of the adverse event is on or after the date/time of IMP dosing. Should any onset date for an adverse event be missing or only a partial date recorded (such that it cannot be determined if the event onset was prior to IMP or not) then it will be assumed that the event is treatment emergent, unless the adverse event stop date indicates otherwise. Any adverse event with an onset date/time earlier than the date/time of IMP dosing will be classified as a pre-treatment adverse event. Any adverse event worsening in severity will be considered as a separate event, starting from the date/time of the updated severity.

Note: Start and Stop times will be used for defining treatment emergence.

If a subject experiences more than one adverse event with the same preferred term, that preferred term will be counted only once in summary presentations. It will be assigned the worst observed severity and the strongest relationship to IMP among those events for the summaries in which those characteristics are considered.

Pre-treatment adverse events will be identified in a subject listing, indicating whether they started before or after inoculation of the challenge virus. Treatment emergent adverse events will be summarised by:

- Treatment group showing number of events, number of subjects with events (also split by severity; mild, moderate, severe, life-threatening, death), number of subjects with SAEs, number of subjects with related events, number of subjects with events leading to discontinuation from the study, number of subjects with events leading to discontinuation of dosing;
- Treatment group, system organ class, and preferred term;
- Treatment group, system organ class, preferred term and severity (Mild / Moderate / Severe);
- Treatment group, system organ class, preferred term and relationship to IMP;

  This Table will only include the subset of adverse events that are judged as being ‘Related’ to treatment, i.e. correspond to adverse events where relationship to IMP is recorded on the adverse event page as being ‘Unlikely to be related’, ‘Possibly related’, ‘Probably related’, ‘Definitely related’, or a relationship is not given. Relationship sub-categories will be displayed in addition to overall numbers.

The summary by relationship to IMP will be repeated for all adverse events by relationship to challenge virus.

Serious adverse events (SAEs) and adverse events directly resulting in withdrawal from study will be listed by treatment group.

In all adverse event summary tables results will be displayed ordered alphabetically by SOC and also preferred term within SOC.

10.8.2. Laboratory Variables

The following haematology, biochemistry, coagulation (if required), cardiac enzyme, thyroid function tests, human immunodeficiency virus and hepatitis A, B and C and urinalysis parameters (as shown within Section 14 of the protocol) will be included within subject listings (and presented in the units as shown) and summary tables where relevant:

- Haematology: platelet count (10^9/L), white blood cell (WBC) count (absolute) (10^9/L), neutrophils (% and absolute (10^9/L)), lymphocytes (% and absolute (10^9/L)), monocytes (% and absolute (10^9/L)), eosinophils (% and absolute (10^9/L)), basophils (% and absolute (10^9/L)), red blood cell (RBC) count (10^12/L), reticulocyte count (% and absolute (10^9/L), haemoglobin (g/L), haematocrit (%), mean corpuscular volume (MCV) (fL), mean corpuscular haemoglobin (MCH) (PG), mean corpuscular haemoglobin concentration (MCHC) (g/L).

- Biochemistry: sodium (mmol/L), potassium (mmol/L), glucose (mmol/L), serum albumin (g/L), chloride (mmol/L), bicarbonate (mmol/L), calcium (mmol/L), uric acid (umol/L), total protein (g/L), creatinine (umol/L), total bilirubin (umol/L), indirect bilirubin (umol/L), direct bilirubin (umol/L), phosphate (mmol/L), blood urea nitrogen (mg/dL), C-reactive protein (CRP) (mg/L), gamma glutamyl transferase (GGT) (IU/L), alkaline phosphatase (ALP) (IU/L), alanine transaminase (ALT) (IU/L), lactate dehydrogenase (LDH) (IU/L), aspartate transaminase (AST) (IU/L), urea (mmol/L).

- Coagulation: prothrombin time (PT) (secs), activated partial thromboplastin time (APTT) (secs).
- Cardiac Enzymes: creatine kinase (IU/L), CK-MB (ug/L), troponin T (ng/L)
- Thyroid Function Tests: Free thyroxine (pmol/L), Thyroid Stimulating Hormone (mIU/L)
- Human Immunodeficiency Virus and Hepatitis A, B and C: HIV-1 and HIV-2 antibodies, hepatitis A antibodies (HepA IgM), hepatitis B surface antigen (HBsAg), hepatitis C antibodies (HCAb).
- Urinalysis: colour, specific gravity, appearance, pH, blood, glucose, leukocytes, ketones, nitrite, protein, urobilinogen, bilirubin.

Laboratory data collected in different units to that shown will be converted to the above specified units (if possible) for presentation in subject Listings.

Summary statistics for absolute and changes from baseline by timepoint will be tabulated, by treatment group, for absolute laboratory parameters (i.e. haematology, biochemistry, coagulation, cardiac enzymes and thyroid function tests).

Laboratory parameters (Haematology, Biochemistry, Coagulation (if required), Cardiac Enzymes, Human Immunodeficiency Virus, Hepatitis A, B and C and Urinalysis) will be included in subject listings. Laboratory values outside the normal range will be identified in subject listings as above or below the normal range.

Unscheduled visit assessments will be included within subject listings.

10.8.3. Vital Signs

Summary statistics for absolute and changes from baseline will be tabulated, by timepoint and by treatment group, for vital signs parameters (systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), respiratory rate (RR) (breaths per minute), heart rate (HR) (beats per minute) and SpO2 (%)) and will be included within subject listings.

10.8.4. Physical Examination

Physical examination findings (both for complete examination and also directed examination assessments) will be included within subject listings.

10.8.5. Spirometry

Summary statistics for absolute values and change from baseline by time point will be tabulated, by treatment group and all subjects, for spirometry parameters (FEV_1(absolute), FEV_1(% predicted), Forced vital capacity (FVC) (absolute), FVC (% predicted), FEV_1/FVC ratio (absolute), FEV_1/FVC ratio (% predicted)) and will also be included within subject listings.

For the calculation of baseline, the mean of all assessments between Day -2 and Day 0 (pre-inoculation), inclusive, will be used.

10.8.6. 12-Lead ECG

Summary statistics for absolute values and change from baseline by time point will be tabulated, by treatment group and all subjects, for ECG parameters (Heart Rate (bpm), PR interval (sec), QRS duration (sec), QT interval (sec), QTc interval (sec), QTcB interval (sec), QTcF interval (sec) and RR interval (sec)) and will also be included within subject listings.

10.9. Pharmacokinetic Analysis

The PK analysis set will be used for all PK presentations. No statistical analysis of PK data will be performed.

10.9.1.1 Plasma EDP-938 PK Parameters

Plasma PK parameters for EDP-938 and its metabolites will be calculated for the first dose and last dose of EDP-938 by PRA, and will be supplied to S-cubed for data presentation purposes. The details of the PK calculations and non-compartmental analysis will be provided in a separate PK Analysis Plan. The summaries described in this section will be repeated for the first and last dose of EDP-938.

Summary statistics for the plasma PK parameters of EDP-938 following administration in healthy adult subjects inoculated with RSV-A Memphis 37b will be tabulated, by treatment group, and will also be included within subject listings. The PK parameters to be summarised will include: C_{max}, T_{max}, $t_{1/2}$, CLss/F, λ_z, Vss/F, C12, C24, $AUC_{0\text{-}last}$, t_{last}, $AUC_{0\text{-}12}$ (BD group only), $AUC_{0\text{-}24}$ (OD group only), $AUC_{0\text{-}tau,}$ and and metabolite-to-parent ratio.

Similarly, summary statistics for the plasma PK parameters of EDP-938 metabolites (i.e. EP-024636, EP-024594, and EP-024595) following repeat dose administration in healthy adult subjects inoculated with RSV-A Memphis 37b will be tabulated, by treatment group, and will also be included within subject listings. The PK parameters for the EDP-938 metabolites to be summarised will include: C_{max}, T_{max}, $t_{1/2}$, λ_z, C12, C24, AUC_{last}, t_{last}, $AUC_{0\text{-}12}$ (BD group only), $AUC_{0\text{-}24}$ (OD group only), and $AUC_{0\text{-}tau}$.

Where a PK parameter is flagged by PRA, the parameter will be included in the Listings but not included in the descriptive summary statistics. Flagging rules are described in the PK Analysis Plan.

In listings, PK data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes. For summary statistics, PK parameters will be rounded to 3 significant figures except for T_{max}, which will be reported with 2 decimals.

10.9.1.2 Plasma EDP-938 Concentrations

Summary statistics for plasma concentration values by time point will be tabulated, by treatment group, for EDP-938 and its 3 metabolites, and will also be included within subject listings.
Plasma concentrations of EDP-938 and its metabolites below the limit of quantification (BLQ) will be set to zero in the computation of mean concentration values. Descriptive statistics will not be presented for a given treatment and timepoint if over half the subjects have values BLQ. Instead, BLQ will display for the median and minimum and, with the exceptions of n and maximum, and all other descriptive statistics will be missing.

The mean (± SD) plasma concentration of EDP-938 and its 3 metabolites (linear and logarithmic (base 10) scale) versus scheduled sampling time profiles, by treatment group, will be displayed graphically. For the semi-logarithmic scale plot of concentrations, the plasma concentration data will not be transformed, but the scale of the y-axis will be in log form, and no error bars will be presented. Mean plots will use the BLQ handling procedures described above.

In addition, individual subject EDP-938 concentration (linear and semi-logarithmic (base 10) scale) verses actual time profiles, by treatment group, will be displayed graphically using spaghetti plots.

For the semi-logarithmic scale plot of concentrations, the plasma concentration data will not be transformed, but the scale of the y-axis will be in log form. Individual plots will use the BLQ handling procedures described above. These plots will be presented on separate axes for after first dose, after last dose, pre-dose troughs, and all timepoints. The time axes will be broken, as necessary, where the scale is not linear (i.e. all timepoints).

10.9.2 Plasma PK (AUC) correlations with viral load RT-qPCR AUC and TSS AUC

For the plots described in this section, the plasma EDP-938 AUC in this section is in relation to the 24-hour period after the last dose of treatment. For the OD group this is AUC_{0-24} and for the BD group an equivalent is estimated from AUC_{0-12} multiplied by 2. Both treatment groups will be presented on the same axis and colour coded.

A scatterplot (together with a regression line and a correlation coefficient) will be produced displaying viral load RT-qPCR AUC (y axis) versus plasma EDP-938 AUC (x axis).

Similarly, a scatterplot (together with a regression line and a correlation coefficient) will be produced displaying (10-item and separately the 11-item) TSS AUC (y axis) versus plasma EDP-938 AUC (x axis).

Secondly, a quartile plot will be produced displaying viral load RT-qPCR AUC box plots (y axis) versus plasma EDP-938 AUC by quartile (Q1, Q2, Q3, Q4) (x axis).

Similarly, a quartile plot will be produced displaying (10-item) TSS AUC box plots (y axis) versus plasma EDP-938 AUC by quartile (Q1, Q2, Q3, Q4) (x axis).

Thirdly, an Emax model plot will be produced displaying viral load RT-qPCR AUC (y axis) versus plasma EDP-938 AUC (x axis).

Similarly, an Emax model plot will be produced displaying TSS AUC (y axis) versus plasma EDP-938 AUC (x axis).

Fourthly, an Emax model plot will be produced displaying viral load RT-qPCR AUC (y axis) versus plasma EDP-938 Ctrough (C12 for BD, C24 for OD relative to the last dose) (x axis).

Similarly, an Emax model plot will be produced displaying TSS AUC (y axis) versus plasma EDP-938 Ctrough (C12 for BD, C24 for OD relative to the last dose) (x axis).

10.9.3 Nasal Wash EDP-938 Concentrations

[redacted]

11.CHANGES TO THE PROTOCOL SPECIFIED ANALYSIS DETAILED IN THE STATISTICAL ANALYSIS PLAN

- The following exploratory endpoints have been defined in the protocol, but will be presented outside of this SAP:
    - [redacted]
    - [redacted]
- The secondary PK endpoints:
    - of $AUC_{0\text{-inf}}$ will not be presented
    - CLss/F and Vss/F will be presented instead of CL/F and Vd/F.
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- The following changes were documented at the BDRM prior to data lock and unblinding of Part 1 of this study. These changes are included in the current SAP Amendment.
    - The following clarifications were made to the definition of viral shedding.

      A subject will fulfil the criteria for viral shedding if:

        - At least two positive ~~quantifiable~~ detections by viral load RT-qPCR assay specific for the challenge virus, reported within two ~~or more~~ consecutive study days

          and/or

        - 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 infectivity assay appropriate for detecting the challenge virus.

    - If an infection is seen (via a positive RT-qPCR value) prior to first dose of IMP but the confirmatory value (as per the first part of the viral shedding definition in Section 4.2 of the protocol) is taken after IMP, then that the subject is declared as infected prior to IMP, and hence will fall into the ITT-A Analysis Set.

- The AUC time period for qPCR was originally based on the assumption that the RT-qPCR assessment at the time of the first IMP dose was taken immediately prior to IMP being given, however, 4 subjects in Part 1 had their qPCR assessment immediately after the first dose of IMP. In order to calculate consistent AUCs, qPCR measurement taken at the time of the first dose of IMP is used as the first value for the AUC.

12.REFERENCES

[1] Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *Br Med J* (1990); 300: 230-5.

(2) Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of American Statistical Association. 1958; 53:457-481.

13.TABLES, FIGURES AND LISTINGS

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