Enanta Pharmaceuticals

EDP 323-101 (ETP-CST-001)

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

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[redacted]

Statistics Department

[redacted]

[redacted]

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Statistical Analysis Plan

Signature

[redacted]			
	Name	**Function**	**Signature**
Written by	[redacted]		
Reviewed by	[redacted]		

Client			
	Name	**Function**	**Signature**
Approved by	[redacted]		

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V1	22/07/2024	[redacted]	NA

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Abbreviations and definitions

AE	Adverse Event
BRDM	Blind Data Review Monitoring
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Coefficient of Variation
CEAE	Challenge Emergent Adverse Events
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EOS	End Of Study
FAS	Full Analysis Set
FSH	Follicule-Stimulating Hormone
GAD-7	Generalized Anxiety Disorder-7
HAI	Haemagglutination inhibition
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HVC	Human Viral Challenge
ICF	Informed Consent Form
ICH	International Council of Harmonization
IMP	Investigational Medicinal Product
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NGS	Next-Gen Sequencing
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
qRT-PCR	quantitative Reverse Transcriptase Ppolymerase Chain Reaction
RiiQ	Respiratory Infection Intensity and Impact Questionnaire
RiiQ-AUC	Area Under the RiiQ score
RR	Respiratory Rate
RVAT	Rapid Viral Antigen Test
SAE	Serious Adverse Event
SAF	Safety Analysis
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure

SDC	Symptom Diary Card
SOC	System Organ Class
SoE	Schedule of Events
Sp02	Peripheral arterial blood saturation
TEAE	Treatment Emergent Adverse Events
TESAE	Treatment Emergent Serious Adverse Events
TSS	Total clinical Symptoms Score
TSS-AUC	Area Under the Curve over time of Total clinical Symptoms Score
TSSPEAK	TSS peak
VL	Viral Load
VL-AUC	Area Under the influenza Viral Load-time Curve
VLPEAK	Viral Load Peak

1 Introduction

This document is the statistical analysis plan (SAP) for the EDP 323-101 study. The purpose of this SAP, based on ICH E9, is to provide a comprehensive and detailed description of the statistical analyses that will be carried out to assess the clinical safety, pharmacokinetics, and efficacy of the study treatment, as outlined in the study protocol version 1.0 (22 June 2023). The SAP pre-specifies the statistical approaches to be used and is validated prior to the study database lock and the unblinding of the randomization schedule to ensure the credibility of the study findings.

2 Highlights from study protocol

2.1 Background/Rationale

Full details of the background and rationale for the study are provided in Section 2 of the protocol.

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

2.2 Study Objectives

Objectives	**Endpoints**
Primary:	
Efficacy	
To evaluate the antiviral activity of EDP-323 compared to placebo in healthy adult participants inoculated with RSV-A Memphis 37b	Reduction in RSV area under the viral load-time curve (VL-AUC) measured by quantitative reverse transcription-polymerase chain reaction (qRT-PCR) in nasal samples
Secondary:	
Efficacy	

• To further evaluate the antiviral activity of EDP-323 compared to placebo in healthy adult participants inoculated with RSV-A Memphis 37b • To evaluate the clinical disease severity in healthy adult participants inoculated with RSV-A Memphis 37b followed by	• Viral load: ○ RSV viral load by qRT-PCR of nasal samples, including: • Reduction in RSV peak viral load (VLPEAK) • Reduction in time to RSV VLPEAK after first dosing • Time to RSV viral load negativity after first dosing

Objectives	**Endpoints**
administration of EDP-323 compared to placebo	• Time to first negative slope of RSV viral load after first dosing • Slope of the RSV viral load over time (clearance rate) from time of RSV VLPEAK to 1, 2, 3, and 4 days later ○ RSV viral load by cell culture (plaque assay) of nasal samples, including: • Reduction in RSV VL-AUC • Reduction in RSV VLPEAK • Reduction in time to RSV VLPEAK after first dosing • Time to RSV viral load negativity after first dosing • Time to first negative slope of RSV viral load after first dosing • Slope of the RSV viral load over time (clearance rate) from time of RSV VLPEAK to 1, 2, 3, and 4 days later

	Clinical symptoms and disease severity: ○ Effect on RSV symptoms using the symptom diary card [SDC]), with endpoints including: • Reduction in area under the total symptom score (TSS)-time curve (TSS-AUC) • Reduction in peak TSS • Time to return to baseline (last assessment before RSV inoculation) TSS • Reduction in time to peak TSS ○ Total weight of nasal discharge (mucus) produced ○ Total number of tissues used
Pharmacokinetics	
• To evaluate the PK profile of EDP-323 (and metabolites) in blood samples in healthy adult participants inoculated with RSV-A Memphis 37b • To characterize the relationship between plasma PK of EDP-323 and VL-AUC (qRT-PCR) and TSSAUC in healthy adult participants	EDP-323 (and metabolites) concentrations and PK parameters in blood samples: maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), apparent systemic clearance (CL/F), terminal elimination rate constant (λ_z), volume of distribution (Vd/F), plasma concentration at 12 hours (C_{12h}), plasma concentration at 24 hours (C_{24h}), area under the concentration-time curve from time 0 to time of last quantifiable concentration (AUC_{last}), area under the concentration-

Objectives	Endpoints
inoculated with RSV-A Memphis 37b	time curve over the dosing interval ($AUC_{0\text{-}tau}$), and area under the concentration-time curve from time 0 to infinity ($AUC_{0\text{-}\infty}$), and other parameters as applicable EDP-323 plasma PK (area under the curve [AUC]) correlations with VL-AUC (e.g., qRT-PCR) and TSS-AUC
Safety	
To evaluate the safety of EDP323 in healthy adult participants inoculated with RSV-A Memphis 37b	• Occurrence of AEs from initial administration of investigational medicinal product (IMP) up to discharge • Occurrence of AEs from initial administration of IMP up to Day 28 follow-up • Occurrence of SAEs from initial administration of IMP up to Day 28 follow-up
[redacted]	
[redacted]	
[redacted]	[redacted]
[redacted]	

2.3 Investigational plan

2.3.1 Study design

This is a randomized, Phase 2a, double-blind, placebo-controlled study to evaluate the safety, PK, and antiviral activity of multiple doses of orally administered EDP-323 against RSV infection in healthy adults after challenge with RSV-A Memphis 37b.
In this study, 2 doses of EDP-323 will be tested: EDP-323 high dose (600 mg QD for 5 days) and low dose (600 mg loading dose for 1 day followed by 200 mg QD for 4 days). The study will have a placebo arm.

Up to 150 healthy male and female participants aged between 18 to 55 years, who are prescreened during the hVIVO generic screening process to document low antibody levels to

RSV and to therefore be susceptible to RSV infection ("serosuitable") will be randomized in one of the 3 treatment arms, with a ratio 1:1:1.

2.3.2 Determination of sample size

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

Before study initiation, the sample size was calculated based on the assumptions of a 55% reduction in qRT-PCR VL-AUC, with a 65.7% coefficient of variation (CV) (based on similar previous studies), for a power of 80% and a 2-sided 5% level of significance (without adjustment for multiple comparisons) and assuming a 70% infectivity rate (based on similar previous studies). On this basis, it was estimated that 27 evaluable RSV infected (intent-totreat infected [ITT-I]) participants per arm and 38 inoculated participants would be sufficient for the study to demonstrate an antiviral affect as measured by qRT-PCR with a power of at least 80% (achieved power computed as 85.5%). However, with the more conservative assumption of a 63% infection rate, 38 recruited participants, resulting in 24 infected participants would allow to detect a 55% relative reduction in qRT-PCR VL-AUC with at least 80% (81.0%) power.

Based on the data from approximately 12 similar studies, the sample size of 38 participants per arm would allow to detect a decrease of 75% in TSS-AUC (CV of 92.9%) and 55% in TSS peak score (CV of 68.8%) with more than 80% power (82.9% and 82.2% respectively) assuming an infection rate of 70% (27 infected participants). Based on these same 12 similar studies, ahe more conservative assumption of a 63% infection rate (24 infected participants) would allow to detect a 75% relative reduction in TSS-AUC and 55% in peak-AUC with respectively 78.2% and 77.4% power.

A new viral grow-up of Memphis 37b is being used for inoculation of subjects in this trial. Because the experimental infections induced by this new viral grow-up may be slightly different quantitatively, blinded evaluation of infectivity rates will be monitored during the study. Sample size adjustments may be made based on these evaluations. Therefore, the study was designed for flexible total subject enrolment, up to 150 subjects.

2.3.3 Study assessments and study plan

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

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

  Results of tests or examinations performed under hVIVO generic screening process may be used to determine eligibility without the need to repeat all assessment prior to

inoculation with challenge agent. Hepatitis and HIV serology should be repeated on the first study day if outside of 56-days window. Screening assessments (including repeats, as required), may be performed up to Day -1 at the discretion of the PI/investigator and in accordance with the design of the study.

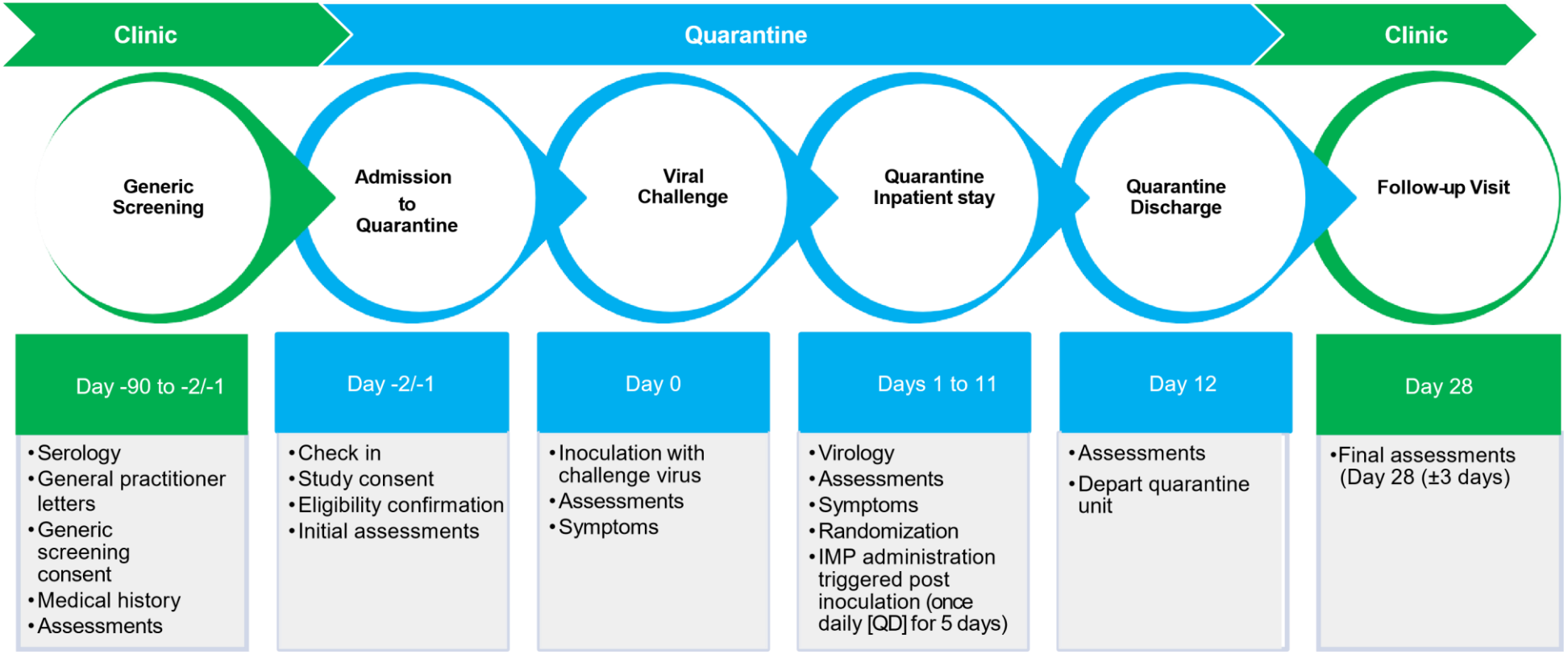
Inpatient Phase:

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

Procedures will include:

- **Pre-human Viral Challenge**:
  - Admission to quarantine unit on Day -2/-1.
  - Baseline assessments will be conducted as per SoE up to Day 0, pre-challenge.
- **Human Viral Challenge**: ○ RSV-A Memphis 37b virus inoculation on Day 0.
- **Post-human Viral Challenge**:
  - Randomization to receive EDP-323 or matched placebo. ○ Administration of IMP (EDP-323 or placebo). IMP administration will be initiated (triggered) by a positive RSV result (measured by qualitative integrative cycler [qic] PCR) between Day 2 and Day 5 AM (nasal sampling twice daily, morning and evening; on Day 5 only in the morning). Dosing will start approximately 12 hours after first detection of RSV. If no positive RSV result is obtained, dosing will start in the evening of Day 5. Duration of treatment with EDP-323 (or placebo) will be 5 days (QD) in the period from Days 2 to 9, with the start day dependent on RSV result.
  - Day 1 onwards and each day – study assessments will be conducted as per SoE.
  - Discharge from quarantine is planned on Day 12 post inoculation.
- **Outpatient Phase:**
  - Follow-up visit: Day 28 (±3 days)

2.3.3.1 Study Schematic: On-study Participant Progression



NOTES:

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

Study Phase	Screening*	Inpatient Phase Quarantine	Outpatient Phase Follow-up	Early Withdrawal (d

2.3.3.2 Schedule of Events (SoE)

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

Study Phase	Screening*	Inpatient Phase Quarantine																Outpatient Phase Follow-up	Early Withdrawal (p)
Study Day (with respect to challenge virus inoculation)	Day -28 to Day -2/-1	Admission Day -2/-1 (o)	Day -1°	Day 0 Pre-Challenge	Day 0 Challenge	Day 0 Post-Challenge	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 28 (±3 days) Final Follow-up	Post-Challenge
Symptom-directed physical examination (including nasal)			(X)	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)			
Vital signs (heart rate [HR], respiratory rate [RR], systolic and diastolic blood pressure [BP], peripheral arterial oxygen saturation [SpO_2]), temperature	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
hVIVO Symptom diary card (SDC) (e)		X	3X	3X			3X	3X	3X	3X	3X	3X	3X	3X	3X	3X	3X	X		
Respiratory Infection Intensity and Impact Questionnaire [RiiQ]) (e)		X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		
24-hour tissue count & nasal discharge weight (f)			X	X			X	X	X	X	X	X	X	X	X	X	X	X		(X)
Product Administration																				
Randomization (g)								(X)	(X)	(X)	(X)									
Investigational medicinal product (IMP) (EDP-323 or placebo) dosing (m)								(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)					

Statistical Analysis Plan

Challenge virus inoculation					X															
Collection of Blood Samples																				

Study Phase	Screening*	Inpatient Phase Quarantine																	Outpatient Phase Follow-up	Early Withdrawal (p)
Study Day (with respect to challenge virus inoculation)	Day -21 to Day -2	Admission Day -2 (o)	Day -1°	Day 0 Pre-Challenge	Day 0 Challenge	Day 0 Post-Challenge	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 28 (±3 days) Final Follow-up	Post-Challenge
Serum follicle-stimulating hormone (FSH) (postmenopausal women)	X																			
Serum beta-human chorionic gonadotrophin (β-HCG) pregnancy test (all female participants)		X																		
Human immunodeficiency (HIV), hepatitis B & C serology	X																			
Hematology (i)	X	X								X			X				X	(X)	X	X
Biochemistry (i)	X	X								X			X				X	(X)	X	X
Coagulation (i)	X																			
Cardiac enzymes	X	X											X				X			
Thyroid function test	X																			
Blood serum for humoral immunity (j)	X	X																	X	(X)
Blood – Pharmacokinetics (PK) (d)								(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		(X)
Blood – Proteomics (exploratory)		X						(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		(X)

Statistical Analysis Plan

Collection of Respiratory Samples																				
Nasopharyngeal swab - Respiratory pathogen screen (k)		X																		
Nasopharyngeal swab - Respiratory syncytial virus (RSV) discharge test (h)																	(X)	(X)		

Study Phase	Screening*	Inpatient Phase Quarantine																	Outpatient Phase Follow-up	Early Withdrawal (p)
Study Day (with respect to challenge virus inoculation)	Day -21 to Day -2	Admission Day -2 (o)	Day -1°	Day 0 Pre-Challenge	Day 0 Challenge	Day 0 Post-Challenge	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 28 (±3 days) Final Follow-up	Post-Challenge
Nasal sampling – Virology (polymerase chain reaction [PCR] & culture) (e, l)			X					2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X		
qualitative integrative cycler (qic) PCR assay for triggered dosing**								2X	2X	2X	X									
Safety Assessments																				
Adverse Events (AEs) (n)		X																		
Concomitant medications (n)		X																		

KEY NOTES FOR SCHEDULE OF EVENTS

(X)	The assessment may be optional, or at the discretion of the principal investigator (PI)/investigator.
X	Once daily, assessments conducted once during the 24-hour period.
2X	Twice daily, assessments conducted twice during the 24-hour period.

3X	Three times daily, assessments conducted 3 times during the 24-hour period.
*	Results of tests or examinations performed under hVIVO generic screening process may be used to determine eligibility without the need to repeat all assessment prior to inoculation with challenge agent. Hepatitis and HIV serology should be repeated on the first study day if outside of 56-days window. Screening assessments (including repeats, as required), may be performed up to Day -1 at the discretion of the PI/investigator and in accordance with the design of the study.
**	Assay to stop once a positive RSV result is obtained.
a	Study-specific consent may occur on the day of admission to the quarantine unit, providing all required eligibility information has been collected through the Health Research Authority approved hVIVO generic screening process.
b	Only the applicable inclusion/exclusion criteria will be reviewed at each time point.
c	Height will be measured at screening only.
d	Time points (hours) for pharmacokinetic (PK) sampling (in blood samples) are as follows: Dose 1: pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15 hours post-dose; Dose 2: pre-dose; Dose 3: pre-dose; Dose 4: pre-dose; Dose 5: pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60, 72 hours post-dose The allowable time windows for the sampling are as follows: • ± 5 minutes from the scheduled time for time points ≤ 2 hours from dosing • ± 15 minutes from the scheduled time for time points > 2 hours to ≤ 24 from dosing • ± 60 minutes from the scheduled time for time points > 24 hours to ≤ 48 from dosing • ± 2 hours from the scheduled time for time points > 48 hours from dosing There is no time window requirement for the pre-dose sample. The pre-dose sample must be taken prior to dose.

e	After the baseline has been set, assessments will be performed at the same time each day (±1 hour from baseline) during quarantine. • Symptom diary card (SDC) baseline: The assessment(s) on Day -1 are considered as the baselines for the subsequent timing windows (assessments on Day -1 will be performed approximately 8 hours [±1 hour] apart). • Respiratory Infection Intensity and Impact Questionnaire (RiiQ) baseline: The assessment on Day -1 are considered as the baselines for the subsequent timing windows. Assessments will be performed once daily at the same time each day (± 1 hour from baseline) during quarantine. • Nasal sample baseline: The AM and PM samples on Day 2 are considered as the baselines for the subsequent AM or PM timing windows (assessments on Day 2 will be performed approximately 12 hours [±1 hour] apart).
	The above baseline requirements are based on an admission on Day -2, if participants are admitted to quarantine on Day -1, appropriate Day 0 time points may be used for baseline timings.
f	Distribution of paper tissues and collection bags will start in the morning on Day -1, with the first collection on Day 0. Thereafter, distribution and collection of tissues will occur daily, at the same time point (±1 hour) in the morning, with tissues distributed 24 hours ahead, until discharge from quarantine.
g	Randomization will take place prior to the first IMP dosing on the day of the first IMP dosing.
h	Viral discharge test (e.g., antigen test) is performed as required by the PI.
i	Blood will be drawn under non-fasted conditions. Repeat bloods may be drawn under fasted conditions if a lipid profile (triglyceride) or glucose is required (at the PI's discretion).
j	Blood serum humoral markers assays specific to the viral challenge agent (i.e., neutralization assay). Serosuitability will be determined from sample collected within 90 days before challenge virus inoculation.
k	Upper respiratory tract (URT) swab (e.g., nasopharyngeal swab) for respiratory virus screen to assess for the presence of respiratory pathogens; if found positive for any pathogen in the panel, the participant will not be eligible for the current quarantine.

l	Post inoculation nasal wash virology samples will be collected and used for quantitative reverse transcription-polymerase chain reaction (qRT-PCR) and viral culture assay (as appropriate). Samples collected between the morning of Day 2 and the morning of Day 5 will also be used for qualitative integrative cycler (qic) PCR until a positive result is received (to support triggered dosing). Samples may be used for related viral genomics[redacted].
m	IMP administration will be initiated (triggered) by a positive RSV result (measured by qicPCR) between Day 2 and Day 5 AM (nasal sampling twice daily, morning and evening; on Day 5 only in the morning). Dosing will start approximately 12 hours (±1 hour) after first detection of RSV. If no positive RSV result is obtained, dosing will start in the evening of Day 5. Duration of treatment with EDP-323 (or placebo) will be 5 days (once daily [QD], approximately 24 hours [±1 hour] apart), with the start day dependent on RSV result.
n	Adverse events (AEs) and concomitant medications are reviewed throughout the study.

o	Assessments performed on Day -2 may be performed on Day -1. For example, participants may be admitted to the quarantine unit on Day -2 or Day -1. If admitted on Day -1, Day -2 assessments will be performed on Day -1, as appropriate.
p	If some of the assessments required as part of the early withdrawal visit have already been performed as per the daily SoE, the completed assessments will not be repeated on the same day as part of early withdrawal visit, unless clinically indicated.
Notes:	• The PI/investigator may perform additional safety assessments as required. • Where any nasal sampling time points occur together, the order of sampling will typically be (1) nasopharyngeal swab followed by (2) nasal wash.

3 Analysis datasets

3.1 Reasons for excluding subjects from analysis datasets

All deviations will be reviewed and adjudicated as either major or minor during the blinded data review meeting before database lock and code break. Reasons for exclusion of participants from analysis sets will be documented in the meeting minutes.

3.1.1 Important protocol deviations

Important protocol deviations are defined as deviations liable to either impact the rights, safety or well-being of the participant or prevent or bias the interpretation of the efficacy results of the study. The following deviations may be considered as important (this list is not exhaustive and will be reviewed at the time of the blind review meeting):

- non compliance with the inclusion or exclusion criteria
- non compliance with the randomization procedure
- non compliance with study treatment
- non compliance with protocol-specified challenge virus inoculation procedures
- missing data for the primary efficacy endpoint (or data collected for the primary efficacy endpoint in a manner diverging from protocol specifications)
- intake of prohibited medication

3.1.2 Not important protocol deviations

All deviations not identified as 'major' will be treated as not important.

3.2 Study treatment discontinuations - Study discontinuations

3.2.1 Participant Withdrawal

See section 7.1 in the study Protocol.

3.2.2 Participant Discontinuation

See section 7.2 in the study Protocol.

3.2.3 Lost to Follow up

See section 7.3 in the study Protocol.

3.2.4 Participant Replacement Policy

See section 7.4 in the study Protocol.

3.3 Analysis sets

3.3.1 Enrolled

A participant will be considered as enrolled into the study once he/she has been inoculated with the challenge virus.

Participants not receiving any dose of IMP, if any, will be included in the Enrolled Analysis Set but only include in the summary columns concerning all the participants since they would not have received study drug.

3.3.2 Intent-to-treat set (ITT) set

All participants having received challenge virus, randomized, and having received at least one dose of IMP. Participants will be analyzed in their randomized group.

3.3.3 Intent-to-treat infected analysis (ITT-I) set

All participants having received challenge virus, randomized, and having received at least one dose of IMP, and meeting the criterion for laboratory-confirmed RSV infection (see Section 5.3.1.4). The ITT-I analysis set will be considered the primary analysis population for efficacy endpoints.

Participants will be analyzed in their randomized group.

3.3.4 Intent-to-treat infected pre-dose (ITT-A) set

All participants having received challenge virus, randomized, and having received at least one dose of IMP, and meeting the criterion for laboratory-confirmed RSV infection (as per ITT-I) while using only assessments prior to taking IMP. The ITT-A analysis set will be considered a secondary analysis population for efficacy endpoints. ITT-A will be a subset of ITT-I.

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.

Participants will be analyzed in their randomized group.

3.3.5 Intent-to-treat infected post-dose (ITT-B) set

All participants having received challenge virus, randomized, and having received at least one dose of IMP, and meeting the criterion for laboratory-confirmed RSV infection (as per ITT-I) but not meeting the criterion for inclusion in ITT-A set. The ITT-B analysis set will be considered a secondary analysis population for efficacy endpoints. ITT-B will be a subset of ITT-I. Participants will be analyzed in their randomized group.

3.3.6 Per protocol (PP) set

All ITT-I analysis set participants who have no major protocol deviations, and who complete the quarantine period up to the final day of quarantine and receive all doses of IMP.
Participant exclusions will be determined at a blinded data review meeting (BDRM), which will take place prior to database lock. The PP analysis set will be considered a secondary analysis population for efficacy endpoints.

Participants will be analyzed in their randomized group.

3.3.7 Safety (SAF) set

All participants having received challenge virus regardless of whether they have received IMP or not.

Participants will be analyzed in their 'as treated' group corresponding to what they actually received.

The 'as treated' group will be derived as follows:

- A participant receiving only placebo doses will be in the placebo 'as treated' group,
- A participant receiving a daily total dose at least once after the loading dose (treatment day 2 to 5) higher than 200mg will be in the High Dose 'as treated' group.
- Other participants receiving at least one dose of EDP-323 will be in the Low Dose 'as treated' group.

As it will not be possible to differentiate between placebo and active capsules in the low dose group except for the loading dose, capsules when mix placebo and active capsules are administered will be considered to have a dose of 200/3= 67mg per capsule for the exposure calculation.

Participants not receiving any dose of IMP, if any, will be included in the Safety Analysis Set but excluded from the summary tables since they would not have received study drug.

3.3.8 Pharmacokinetics (PK) set

All ITT analysis set participants with at least one post-dose PK result. The PK analyses will be performed on the PK analysis set.

4 Endpoints/Variables/Assessments for analysis

4.1 Efficacy endpoints

4.1.1 Primary efficacy endpoint

This study has one primary endpoint:

Area under the viral load-time curve (VL-AUC) measured by quantitative reverse transcriptionpolymerase chain reaction (qRT-PCR) in nasal samples.

4.1.2 Secondary efficacy endpoints

4.1.2.1 RSV viral load by qRT-PCR of nasal samples

Several endpoints are based on the viral load measured by qRT-PCR:

- RSV peak viral load (VLPEAK)
- Time from the last measurement collected prior to the first dose of IMP to RSV VLPEAK
- Time from the last measurement collected prior to the first dose of IMP to RSV viral load negativity
- Time from the last measurement collected prior to the first dose of IMP to first negative slope of RSV viral load
- Slope of the RSV viral load over time (clearance rate) from time of RSV VLPEAK to 1, 2, 3, and 4 days later

4.1.2.2 RSV viral load by cell culture (plaque assay) of nasal samples

Several endpoints are based on the viral load measured by cell culture:

- RSV VL-AUC
- RSV VLPEAK
- Time from the last measurement collected prior to the first dose of IMP to RSV VLPEAK
- Time from the last measurement collected prior to the first dose of IMP to RSV viral load negativity
- Time from the last measurement collected prior to the first dose of IMP to first negative slope of RSV viral load
- Slope of the RSV viral load over time (clearance rate) from time of RSV VLPEAK to 1, 2, 3, and 4 days later

4.1.2.3 Clinical symptoms and disease severity

The main total symptom score (TSS) will be based on 10 items (see section 0) and referred to as TSS. A total symptom score using 11 items will also be derived and referred to as TSS11 (see section 0). The symptom endpoints will be derived both using TSS and TSS11.

The Total Symptom Score is calculated from the symptom diary card (SDC).

Area under the total symptom score (TSS)-time curve (TSS-AUC)

- Peak TSS
- Time to resolution from peak symptom
- Time from the last measurement collected prior to the first dose of IMP to peak TSS
- Total weight of nasal discharge (mucus) produced

- Total number of tissues used

[redacted]

4.2 Pharmacokinetic endpoints

This study has 2 PK endpoints:

- Plasma EDP-323 (and metabolites) PK concentrations and PK parameters: maximum plasma concentration (Cmax), time to maximum plasma concentration (tmax), terminal half-life (t1/2), apparent systemic clearance (CL/F), terminal elimination rate constant (λz), volume of distribution (Vd/F), plasma concentration at 12 hours (C12h), plasma concentration at 24 hours (C24h), area under the concentration-time curve from time 0 to time of last quantifiable concentration (AUClast), area under the concentration-time curve over the dosing interval (AUC0-tau), and area under the concentration-time curve from time 0 to infinity (AUC0-∞), and other parameters as applicable
- EDP-323 plasma PK AUC correlations with VL-AUC (e.g., qRT-PCR) and TSS-AUC

4.3 Safety

The safety and tolerability will be evaluated by the monitoring of:
occurrence of AEs and SAEs,

- complete and symptom-directed physical examinations,
- vital signs (heart rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), peripheral arterial oxygen saturation (SPO2)),
- clinical laboratory results (haematology, coagulation, biochemistry, serology (HIV, hepatitis), thyroid function, cardiac enzymes, urinalysis, urine pregnancy test),

- spirometry,
- 12-lead electrocardiogram (ECG),
- tympanic temperature, alcohol breath test concomitant medications.

Safety and tolerability will be assessed over the whole study period, up to EOS (planned on Day 28 ± 3).

Secondary safety endpoints are:

- Occurrence of AEs from initial administration of IMP up to discharge
- Occurrence of AEs from initial administration of IMP up to Day 28 follow-up
- Occurrence of SAEs from initial administration of IMP up to Day 28 follow-up

[redacted]

4.3.1 Adverse events

AEs will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA Preferred Term (PT) and System Organ Class (SOC).

Challenge Emergent Adverse Events (CEAE) will be defined as any adverse event that occurs from the time of viral challenge until last study visit (Day 28 ± 3, or date of last unscheduled visit), i.e.:

- An AE that was not present prior to the viral challenge, or
- An AE that was present prior to the viral challenge and increased in intensity after the viral challenge or
- An AE that was present prior to the viral challenge, with no change in the intensity but with a drug relationship that became related after the viral challenge.

Treatment Emergent Adverse Events (TEAE) will be defined as any adverse event that occurs from the time of first study treatment dose administered to the subject until last study visit (Day 28 ± 3, or date of last unscheduled visit), i.e.:

- An AE that was not present prior to receiving the first dose of IMP, or
- An AE that was present prior to receiving the first dose of IMP and increased in intensity after the first IMP administration, or

- An AE that was present prior to receiving the first dose of IMP, with no change in the intensity but with a drug relationship that became related after the first IMP administration.

Three periods will be defined for CEAE and TEAE reporting:

- Period 1 between the challenge virus inoculation on Day 0 and the first dose of IMP, on the latest on Day 5.
- Period 2 from first dose of IMP until the discharge of the participant from quarantine (either as scheduled on Day 12 or later, on PI's decision).
- Period 3 from the actual discharge from quarantine until EOS (Day 28 ± 3, or date of last unscheduled visit).

CEAE will be during Period 1, 2 or 3 and TEAE during Periods 2 and 3.

Participants who did not receive the viral challenge will not have CEAE.

Participants who did not receive any dose of IMP will not have any TEAE in Periods 2 and 3. Participants prematurely withdrawn before actual discharge of the given participant from quarantine will not have any TEAE in Period 3.

Handling of missing or incomplete dates in the definition of treatment emergence and attribution between the 3 periods is provided in Section 5.3.4.1.

The grading of the severity of the AEs will use the Common Terminology Criteria for Adverse Events (CTCAE) for Grading the Severity of Adverse Events, Version 5.0. November 2017. For AEs that do not appear in the CTCAE Table, the severity will be determined according to the definitions in Table 1.

Table 1- Classification of Adverse Events Severity

Grade	Definition
Grade 1	Mild ; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting ageappropriate instrumental ADL[a]
Grade 3	Severe or medically significant but not Immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL[b]
Grade 4	Life-threatening consequences; Urgent intervention indicated
Grade 5	Death related to AE

[a] 'Instrumental ADL' refers to activities of daily living such as preparing meals, shopping for groceries or clothes, using the telephone, and managing money. [b]'Self-care ADL' refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.

A Challenge Emergent Adverse Events (CEAE) will be defined as any adverse event that occurs from the time of challenge to the subject until last study visit (Day 28 ± 3).

Serious adverse events (SAE) are those AEs that put the life of the subject at risk or that cause serious or permanent damage to the subject's health. An AE is to be recorded and reported as SAE in the event of any of the following:

- AE results in death.
- AE is life-threatening (i.e. constitutes an immediate threat to the subject's life).
- AE results in hospitalization of the trial participant or prolongs an existing hospitalization.
- AE results in persistent or significant disability or incapacity.
- AE is a congenital anomaly or birth defect.
- AE is another medically important condition: an AE that does not result in death, threaten life, require hospitalization, or result in persistent/significant disability, but jeopardizes the participant and requires medical or surgical intervention to prevent one of the aforementioned outcomes.

An SAE at least possibly related to the IMP will be considered as a Serious Adverse Reaction (SAR).

4.3.2 Laboratory variables

Urinalyses are to be performed during screening (Day -90 to Day -1), when entering quarantine at Day -2/-1, at Day 12 and at follow-up visit (Day 28 +/- 3).
Alcohol breath test and urine drugs of misuse and cotinine screen are to be performed during screening (Day -90 to Day -1), when entering quarantine at Day -2/-1, and at follow-up visit (Day 28 +/- 3).
Biochemistry and haematology are to be performed during screening (Day -90 to Day -1), when entering quarantine at Day -2/-1, at Day 4, Day 6, Day 11, possibly at Day 12 and at follow-up visit (Day 28 +/- 3).
Cardiac enzymes are to be measured during screening (Day -90 to Day -1), when entering quarantine at Day -2/-1, at Day 7 and at Day 11.

- Biochemistry: Sodium, Potassium, Glucose, Albumin, Chloride, Bicarbonate, Calcium, Uric acid, Total protein, Creatinine, bilirubin (Total, direct, and indirect), Inorganic phosphate, Blood urea nitrogen, C-reactive protein, Gamma glutamyl transferase, Alkaline phosphatase, Alanine aminotransferase (ALT), Lactate dehydrogenase, Aspartate aminotransferase (AST), Urea
- Haematology: Platelet count, White blood cell count (absolute and differential: Neutrophils, Lymphocyte, Monocytes, Eosinophils, Basophils), Red blood cell count, Reticulocyte count (% and absolute), Haemoglobin, Haematocrit, Mean corpuscular volume, Mean corpuscular haemoglobin, Mean corpuscular haemoglobin concentration

- Cardiac enzymes: creatine kinase, troponin
- Urinalysis: Color, Specific gravity, Appearance, pH, Presence of blood, glucose, leukocytes, ketones, nitrites, proteins, urobilinogen, and bilirubin by dipstick ○ If the dipstick yields clinically significant abnormal results: microscopy, culture, and sensitivity examination
- Alcohol breath test and urine drugs of misuse and cotinine screen

4.3.3 Other safety endpoints

4.3.3.1 Physical examinations

Complete physical examinations will be conducted to include a full systemic assessment and will be performed during screening, at admission, at Day 12 and at Day 28.
Directed physical examinations will be conducted as deemed appropriate by the investigator and may include (as applicable) examination of the ears, nose, throat, and respiratory system/chest (via stethoscope). It will be conduct at any time during quarantine if deemed necessary, and during follow-up visit at Day 28.

Assessment and grading of any URT (nasal discharge, otitis, pharyngitis, sinus tenderness) and LRT symptoms (abnormal breath sounds externally [e.g., stridor, wheezing] and on chest auscultation [rhonchi, crepitations, or other]) will be performed, as applicable. Physician reported assessments of challenge agent-related illness will be graded in accordance with its intensity and documented in the source data.
Following challenge agent inoculation all unexpected (in the opinion of the PI/investigator) symptom-directed physical examination findings will be captured as AEs, along with all other occurrences that meet the criteria for an AE.
Following challenge agent inoculation, additional symptoms that are not available in the list of symptoms of the symptom diary card and are deemed to be clinically significant (in the opinion of the PI/investigator) will be captured as AEs.

4.3.3.2 Vital signs

Vital signs assessments will be recorded as follows during screening phase (D90 to Day -2/-1), admission (Day -2 / -1), pre-HVC (day 0), every day from Day 1 to Day 12 or discharge and at follow-up visit (Day 28 +/- 3):

- Heart rate will be recorded in beats per minute.
- Respiratory rate: respirations will be counted and recorded as breaths per minute.
- Blood pressure: systolic and diastolic blood pressure will be measured in millimeters 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.
- Tympanic temperature

Study specific normal ranges are provided in Table 2. If a result is out of the normal range and meets the criteria for an AE, the severity of the AE will be determined based on the CTCAE grading table November 2017.

Table 2 - Vital sign normal ranges

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

Source: protocol, appendix 4: Normal ranges.

4.3.3.3 Electrocardiograms (ECG)

The following 12-lead ECG parameters will be performed at screening, admission (Day -2/-1), Day 7, Day 11 and Day 28:

- Heart rate in beats per minute
- QRS, PR interval, QT, QTc in milliseconds

Study specific normal ranges are provided in Table 3.

Table 3 - ECG normal ranges

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

Source: protocol, appendix 4: Normal ranges.

4.3.3.4 Concomitant medications

Concomitant medication data will be coded according to the latest WHO Drug dictionary. Concomitant medications are defined as any medication which was taken at any time on or after the start of study treatment, i.e.:

- Started before or on first IMP intake and still ongoing at first IMP intake
- Started after first IMP intake

All medication started before first IMP intake will be considered prior medications. Medications started before or on first IMP intake and still ongoing at first IMP intake will be considered both prior and concomitant medications.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5 Statistical and Analytical Methods

5.1 General statistical considerations

The statistical analyses are performed in accordance with the ICH E9 guideline and other relevant guidance.

The statistical analyses will be performed by an external Contract Research Organization (CRO), [redacted] under the responsibility of the Sponsor. Apart from Kaplan-Meier analysis, no figures will be produced by [redacted].

5.1.1 Presentation of results

The following descriptive statistics will be presented:

- For quantitative variables: number of available values (N), number of missing values, mean (Mean), standard deviation (SD), coefficient of variation (CV), Standard Error of the Mean (SE), median (Median), Q1 (or first quartiles), Q3 (third quartiles), minimum (Min), maximum (Max) values. When relevant, confidence intervals will be calculated for the mean (Student CI) or the median (Hahn & Meeker 1991). For prespecified endpoints, the geometric mean (Geometric mean) and standard deviation (GSD) will also be presented.

- For qualitative variables: number of available values, number of missing values, number and percentage of observations in each category of the variable. Percentages

will be calculated using the number of available data as the denominator (i.e., not including missing values). When relevant, Cis will be computed. If not otherwise specified in the SAP, the Wilson Score method will be used to compute Cis for proportions.

Except for safety, tables and figures will be presented by randomized treatment arm (active treatment high dose, active treatment low dose, placebo). For the safety analyses, tables and Figures will be presented by actual treatment arm tables. Results will also be presented for pooled EDP group (high dose and low dose together). For demographic and baseline characteristics analyses, the results will also be presented for all participants together. Listings will be presented by subject ID and according to the AdaM structure. All deliverables will be produced in single rtf format and in combined pdf format, using Courier New 9 font.

In the results tables and figures, the arms will be called as followed:

- EDP-323 - High dose
- EDP-323 - Low dose
- POOLED EDP
- Placebo
- All

Note: when the geometric mean is produced and the endpoint can have raw value of 0, an appropriate constant will be added to all raw value (see Section 0). The constant value used will be documented in a footnote.

5.1.2 Significance testing and estimation

5.1.2.1 Between group comparisons

All hypotheses will be tested using two-sided test at a 5% level of significance (alpha).

The differences will be compared between each active groups and placebo group using an ANCOVA with treatment group as main effect and baseline values as a covariate. The treatment baseline value will be used (see Section 5.3.1.1). The LS means of the treatment differences for each comparison, with the corresponding 95% CI and p-value will be presented. A comparison between pooled active groups and placebo will be performed. The equivalent Wilcoxon-Mann-Whitney test p-values will also be presented.

For endpoints that require a geometric mean to be produced, and those endpoints can have raw values of 0 (zero), the GM calculation will add an appropriate constant value to all raw values prior to logging and will subtract that constant value from the final calculated antilogged mean. The constant value used will be documented in the footnote of the tables. The value is

typically 1 however it may be another small value which is in line with the scale of the data should a value of 1 be unsuitable. The GM and GSD calculation are detailed in Section 0.

For categorical variables, differences in absolute frequency and/or relative risks will be presented, with their 95% two-sided CIs using Miettinen-Nurminen score confidence limits. The Chi-square test (or Fisher exact test in case of low number) will be used to compare frequencies between groups.

5.1.2.2 Control of overall type-I error

Note that different hypotheses (1 for each IMP dosing regimen and one for pooled IMP regimen) will be tested using the same placebo group (see section 5.5.1.1[redacted]). Considering that the study is a Phase 2a study, aiming at providing proof of concept of the activity of EDP-323, no adjustment for multiple testing will be performed.

Some secondary endpoints will also be compared between randomized groups using inference tests, but these results will have to be regarded as illustrative only and no definitive conclusions should be drawn from them, because of the potential risk of type-I error (false positive).

5.2 Sequence of analyses

One single, final, analysis is planned after all participants have completed the EOS (or early withdrawal) visit, after data management is complete and after the blind data review and database lock.

5.3 Data handling conventions

5.3.1 Definitions

5.3.1.1 Baseline definitions

Two baselines will be defined:

- The first baseline (challenge baseline) is defined as the last non-missing measurement before viral challenge. This will usually correspond to the measurement performed during preHVC visit on Day 0. In case of missing value at Day 0 the last available value recorded during previous visits will be used as baseline value. If no data are available prior to viral challenge, it will be considered as a missing value.
- The second baseline (treatment baseline) is defined as the nearest planned assessment to the first dose of study IMP, on the same day. If no data are available at this planned assessment, it will be considered as a missing value.

If all pre-challenge measurements are missing the challenge baseline will be considered as missing, and no change from baseline and no percentage change from baseline will be computed.
If the nearest planned assessment to the first dose of study IMP is missing, the treatment baseline will be considered as missing. The corresponding participant will not be included in the ANCOVA analysis. All cases will be discussed in BDRM.

For the presentation of the change from baseline, the challenge baseline will be considered. For adjustment on baseline results in ANCOVA, the treatment baseline will be used.

Note: for VL-AUC, the baseline values will refer to the corresponding VL values (either measured by qRT-PCR or by cell culture). Similarly, for TSS-AUC or RiiQ-AUC, the baseline values will refer to the corresponding raw score.

5.3.1.2 Assessments beyond Day 12

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. The exception concerns the PK samples, that can be collected on Day 12 pm.

5.3.1.3 Quarantine discharge

Unless otherwise specified, Quarantine Discharge refers to the actual quarantine discharge day regardless of whether discharge from quarantine occurred as scheduled on Day 12, or later following the PI's decision to extend the quarantine period for a given participant.

5.3.1.4 Laboratory-confirmed infection

A participant will fulfil the criteria for laboratory-confirmed RSV infection if:

- At least 2 positive detections (≥ lower limit of detection [LLOD]) by viral load qRT-PCR assay specific for the challenge virus, reported within 2 consecutive study days, starting from Day 2 (am) up to planned discharge from quarantine (Day 12, am).

And/or

- One positive detection by viral load qRT-PCR assay, specific for the challenge virus, in which an aliquot of the same sample has also tested positive in a cell-based infectivity assay appropriate for detecting the challenge virus, starting from Day 2 (am) up to planned discharge from quarantine (Day 12, am).

In all the document, it will be called laboratory confirmed infection.

More precisely, to define the lab-confirmed RSV infection with the first condition presented before, we will use the rule set out in Table 4 below where day n to n+1 are 2 consecutive days within Day 2 am and Day 12 am. qRT-PCR assessments are supposed to be performed every 12 hours. Thus, within 2 consecutive days, it is expected to have 4 tests performed.

Table 4: Decision rule to define infection for qRT-PCR

qRT-PCR				
Assessment 1 – Day n	Assessment 2 – Day n	Assessment 1 – Day n+1	Assessment 2 – Day n+1	Condition met for qRT-PCR-confirmed RSV infection?
Detectable	Detectable	Detectable	Detectable	Yes
Detectable	Not Detectable	Detectable	Detectable	Yes
Detectable	Detectable	Not Detectable	Detectable	Yes
Detectable	Detectable	Detectable	Not Detectable	Yes
Detectable	Not Detectable	Not Detectable	Detectable	Yes
Detectable	Detectable	Not Detectable	Not Detectable	Yes
Detectable	Not Detectable	Detectable	Not Detectable	Yes
Detectable	Not Detectable	Not Detectable	Not Detectable	No
Not Detectable	Detectable	Detectable	Detectable	Yes
Not Detectable	Not Detectable	Detectable	Detectable	Yes
Not Detectable	Detectable	Not Detectable	Detectable	Yes
Not Detectable	Detectable	Detectable	Not Detectable	Yes
Not Detectable	Not Detectable	Not Detectable	Detectable	No
Not Detectable	Detectable	Not Detectable	Not Detectable	No
Not Detectable	Not Detectable	Detectable	Not Detectable	No
Not Detectable	Not Detectable	Not Detectable	Not Detectable	No

In case of missing qRT-PCR results:

- If there are at least 2 assessments over 2 consecutive days that are detectable, the condition will be met.
- otherwise, it will be discussed in BRDM, except if at least 1 viral culture assessment is detectable, for a matching detectable RT-qPCR result, in which case the condition will be met.

5.3.2 Retest, Outliers

5.3.2.1 Retests

The retests will be managed as follow:

- Any retest before baseline: the last available value before baseline will be used as the baseline (see 5.3.1.1).
- Any other retest: no value will be used except if otherwise specified during the data review meeting. All available values (including retest values) will be presented in the data listings.

5.3.2.2 Outliers

All available data points will be included in analysis unless a clear reason is available to exclude data. All outlier data will be reviewed during the data-review meeting and decisions regarding their use in the statistical analyses will be made.

5.3.3 Values below detection limits

Unless otherwise specified, any data recorded as Detected, Not detected, Invalid, N/A or NDA will be presented as such in listings but will be replaced with the Assigned value described in the following table:

Table 5- Rules for handling viral load results

Analysis	Assay (units)	Assay LLOD	Assay LLOQ	Assay Reporting	
				Reported result	SAP assigned value
RSV titer (Viral Load)	RSV Viral Culture assay (Log_{10} PFU/mL assay)	1.02	2.02	Value	Use reported value
				DETECTED	1.01 log_{10} PFU/mL
				NOT DETECTED	0
				>X.XX*	X.XX*
				INVALID	Missing data point
				N/A	Missing data point
RSV titer (Viral		N/A	3.19**	Value	Use reported value
				DETECTED	1.60 log_{10} copies/mL

Load)	qRT-PCR (log_{10} copies/mL)			NOT DETECTED	0
				>X.XX*	X.XX*
				INVALID	Missing data point
				N/A	Missing data point
RSV antibody titer	RSV Neutralization Assay	10	156	Value	Use reported value
				NDA	10
				<156	156
				>XXXX*	XXXX
Analysis	Assay (units)	Assay LLOD	Assay LLOQ	Assay Reporting	
				Reported result	SAP assigned value
	(virus focus reduction neutralization assay)			INVALID	Missing data point
				N/A	Missing data point

LLOD, Lower Limit of Detection; LLOQ, Lower Limit of Quantification; N/A, not applicable; NDA, no detectable antibody;

* A greater than (>) value may be reported if insufficient sample to perform a re-test to obtain a quantifiable result. The value reported will be the assigned value.

**The LLOQ is defined as a cycle threshold (Ct) value of 32.53. This equated to 3.19 Log10 copies/mL by utilization of a target specific copy number standard curve included in each assay run of the assay validation.

5.3.4 Missing data

5.3.4.1 Missing or incomplete dates

For calculation / sorting / assignation based on dates (e.g., treatment emergent AEs, assignation of AEs between periods, concomitant medications, etc.), the following rules will apply:

- In case of AE with missing start date, it could be included in different analysis periods at the same time. If the AE could have started in multiple periods based on all the available information, it will be analysed in all the possible periods (i.e.; for a AE with complete missing start date and end date after end of quarantine, the AE will belong to the 3 periods, for an AE with only the information that the AE started the month of treatment start and inoculation but before the end of quarantine, the AE will belong to period 1 and period 2)
- Medication with missing/incomplete start date will be assumed to have occurred after the study treatment except when the partial onset or end date indicates differently.

- Medication with missing/incomplete end date not ongoing at the end of trial will be assumed to have occurred after the study treatment except when the partial end date indicates differently.
- Medical history or disease diagnosis with missing/incomplete date will be assumed to have occurred before inoculation and study treatment except when the partial onset date or other available data indicates differently.
- Assignations based on dates will be reviewed during the data review meeting.
- Missing or partial start or end dates of IMP administration, if any, will be reviewed during the BDRM.

5.3.4.2 Missing Viral Load and Total Symptom Score data

Missing Viral Load and Total Symptom Score data may impact the derivation of some of the study endpoints (AUC, peak and duration-related endpoints). Rules on how to derive these endpoints in the presence of missing data are provided in Section 0. These rules are provided as a general guidance, but each specific case will be reviewed during the Blinded Data Review Meeting, and specific decisions can be taken that overrule these general rules. Decisions to derive and how to derive these endpoints in the presence of missing data will be documented in the BDRM minutes together with the rationale for each decision.

5.3.4.3 Other missing data

No other missing data will be imputed except if otherwise specified in the SAP. Any other mechanisms to handle missing data will be outlined within the relevant endpoints section.

5.3.5 Windows for time points

All visits will be analyzed as entered in the database except if otherwise specified during the data-review meeting.

5.3.6 Unscheduled visits

Unscheduled visit measurements may be used to provide a measurement for a baseline or endpoint value, if appropriate, according to their definition. Other unscheduled visits data will not be analyzed, except if otherwise specified during the data review meeting, but corresponding data will be presented in the individual data listings and any relevant safety data will be described in the CSR.

5.4 Planned analysis

The list of statistical Tables, Figures and Listings are provided in Section 11.
If several analysis sets consist of the same participants, analyses will not be repeated on all sets.

5.4.1 Subject disposition and study discontinuations

Subject disposition will be described using a table (Statistical table 14.1.1). The following variables will be tabulated by randomized arm and overall:

- Number of participants receiving challenge virus
- Number of participants randomised
- Number of participants receiving at least 1 dose of IMP
- Number of participants receiving all doses of IMP

Analysis sets will be tabulated, overall and by randomized arm along with reasons for exclusion from the ITT, ITT-I, ITT-A, ITT-B, PP, and SAF sets (Statistical Table 14.1.2.1) on the Enrolled set. Analysis set will also be tabulated per quarantine (Statistical Tables 14.1.2.2 to 14.1.2.8). Individual data on the inclusion to/exclusion from each of the defined analysis sets will be provided in Listing 16.2.2.

Study duration and premature study discontinuation will be summarized using the following variables on the Enrolled Set, overall, by pooled active arm and by randomized arm:

- Number of participants who completed/discontinued the quarantine
- Number of participants who completed/discontinued the study
- Reason for study discontinuation
- Study duration

The results will be included in Statistical Table 14.1.1

Individual data on end of study information and reasons for discontinuation will be provided in Listing 16.2.1.

Visit dates (including date of consent) will be presented in Listing 16.2.4.14. The list of randomisation will be presented in Listing 16.2.3.

5.4.2 Protocol deviations

All protocol deviations classified during the blinded data review meeting according to definitions provided in Section 3.1.1 (Important protocol deviations) and 3.1.2 (Not Important protocol deviations) will be tabulated by randomized arm for the Enrolled set (Statistical Table 14.1.3). Individual data on protocol deviations will also be provided in Listing 16.2.4.

5.4.3 Demographics and baseline characteristics

The following demographics variables will be summarized by randomized on the ITT, ITT-I, ITTA, ITT-B, PP, and SAF analysis sets (Statistical Table 14.1.4.1 to Table 14.1.4.6) and individual data provided in Listing 16.2.4.1:

- Sex
- Age
- Race
- Ethnicity

The following baseline characteristics will be summarized by treatment arm on the ITT-I analysis set for tables and listed on the Enrolled analysis set:

- Weight, height (in cm) and BMI (Statistical Table 14.1.5 and Listing 16.2.4.2)
- Alcohol breath test and drugs of abuse and cotinine use (Statistical Tables 14.1.6 and 14.1.7 and Listings 16.2.4.3 and 16.2.4.4)
- Alcohol and smoking history (Statistical Tables 14.1.8 and 14.1.9 and Listings 16.2.4.5 and 16.2.4.6)
- Urine pregnancy test, serum follicle-stimulating hormone (FSH) levels and serum betahuman chorionic gonadotrophin (β-HCG) pregnancy test (Listing 16.2.4.7)
- HIV, hepatitis B and C, coagulation and thyroid function (Listing 16.2.4.8). Eligibility criteria will be presented respectively in Listing 16.2.4.9.

Nasal swab respiratory pathogen screen data will be presented in Listing 16.2.4.10.

5.4.4 Medical history – Previous medications

Medical history for each participant will be reported in Listing 16.2.4.11. They will be tabulated by randomized arm and overall on the ITT set (Statistical Table 14.1.10).

Prior medications for each participant will be reported in Listing 16.2.4.12 (together with concomitant medications).

5.4.5 Concomitant medications

Concomitant medications for each participant will be reported in Listing 16.2.4.12.1 (together with prior medications). Concomitant medications will be summarized by randomized arm and overall on the ITT set (Statistical Table 14.1.11).

5.4.6 Concomitant procedures

Concomitant procedures for each participant will be reported in Listing 16.2.4.12.2.

5.4.7 Compliance

The study consists of 5 doses of IMP, corresponding to [redacted] capsules ([redacted] capsules per day), administered once daily for 5 consecutive days. The expected number of capsules will be calculated using the start/stop dates and times for each participant. Compliance with IMP will be derived as:
(number of capsule received/number of capsules expected) * 100

Compliance with IMP (active treatment high dose, active treatment low dose, placebo) will be computed on the ITT set by randomized arm (Statistical Table 14.1.12) by assessing the proportion of participants receiving <25%, ≥25% but <50, ≥50% but <75%, and ≥75% of the IMP dose as prescribed.

5.5 Efficacy analyses

All the efficacy analysis will be performed on the ITT-I set. For several endpoints, sensitivity analysis may be performed on ITT-A, ITT-B and PP sets, if more than 5% of the patients are assigned differently than in the ITT-I set.
Pooled active groups results will be presented for all efficacy analyses. Derived efficacy response data will be listed in 16.2.6.4.

5.5.1 Primary efficacy analysis

5.5.1.1 Statistical hypotheses for primary efficacy analysis

The main study hypothesis is that treatment with EDP-323 will show an antiviral effect demonstrated by a significant reduction in RSV VL-AUC (measured by qRT-PCR) compared to placebo.

As stated in section 5.1.2, this hypothesis for each dosing regimen and the pooled EDP-323 regimens will be tested using a 2-sided type 1 error rate of 0.05, without adjustment.
The following statistical hypotheses will be tested:

- *H1*: VL-AUC of RSV challenge virus (Active treatment 1) ≠ VL-AUC of RSV challenge virus (placebo) vs *H0*: VL-AUC of RSV challenge virus (Active treatment 1) = VL-AUC of RSV challenge virus (placebo)
- *H1*: VL-AUC of RSV challenge virus (Active treatment 2) ≠ VL-AUC of RSV challenge virus (placebo) vs *H0*: VL-AUC of RSV challenge virus (Active treatment 2) = VL-AUC of RSV challenge virus (placebo)
- *H1*: VL-AUC of RSV challenge virus (Pooled EDP-323 treatment) ≠ VL-AUC of RSV challenge virus (placebo) vs *H0*: VL-AUC of RSV challenge virus (Pooled EDP-323 treatment) = VL-AUC of RSV challenge virus (placebo)

5.5.1.2 Statistical methods for primary efficacy analysis

The calculation of the VL-AUC will be performed on log10-transformed PCR data, measured twice a day from the measurement collected at the time of the first dose of IMP to Day 12 (am), using the trapezoidal summation rule based on actual time intervals in hours (see Section 0). Results below the LLOQ and LLOD will be given values as detailed in Table 5.

The VL-AUC will be compared between each active group and placebo group using an ANCOVA with treatment group as main effect and baseline values as a covariate. The treatment baseline value will be used (see Section 5.3.1.1). The LS means of the treatment differences for each comparison, with the corresponding 95% CI and p-value will be presented. The equivalent Wilcoxon-Mann-Whitney test p-values will also be presented.

For exploratory purpose, the comparison between each active treatment arms will also be presented.

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;
```

Note: a separate model will be fit for each comparison (active group high dose vs placebo, active group low dose vs placebo…), using only the data relevant to this comparison. Results will be presented in Statistical Table 14.2.1.1.1.1.

Sensitivity analysis will be performed using alternative definitions of AUC (AUC variant 1 to 3, see Section 6). Results will be presented in Statistical Tables 14.2.1.1.2.1, 14.2.1.1.3.1 and 14.2.1.1.4.1.

This analysis will be repeated on ITT-A, ITT-B and PP sets (Statistical Tables 14.2.1.1.1.2, 14.2.1.1.1.3, 14.2.1.1.1.4, 14.2.1.1.2.2, 14.2.1.1.2.3, 14.2.1.1.2.4, 14.2.1.1.3.2, 14.2.1.1.3.3, 14.2.1.1.3.4, 14.2.1.1.4.2, 14.2.1.1.4.3, 14.2.1.1.4.4).

Viral load from qRT-PCR will also be described by day (relative to treatment baseline assessment) and by time point, with a line plot of VL mean values over time (Statistical Tables 14.2.1.2.1 to 14.2.1.2.4 and Figures 14.2.1.1 to 14.2.1.4).

The mean values (+/- 1 Standard Error (SE)) will be displayed graphically by day (relative to treatment baseline assessment) and assessment, and treatment group. In order to calculate the timepoint that each assessment will be presented against, the RT-qPCR 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). Timepoint 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.

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.

Viral load data will be listed in 16.2.6.1.

VL-AUC will also be described by quarantine group (main AUC and variants 1 to 3) on the ITTI set (Statistical Tables 14.2.1.3.1 to 14.2.1.3.4).

5.5.2 Secondary efficacy analysis

5.5.2.1 VL-AUC measured by cell culture

The calculation of the viral load AUC (VL-AUC) will be performed on log10-transformed viral culture assessment measured twice a day from the measurement collected at the time of the first dose of IMP to Day 12 (am), using the trapezoidal summation rule based on actual time intervals in hours (see Section 6). Results below the LLOQ will be given values as detailed in Table 5.

This outcome will be analysed as the primary efficacy endpoint on the ITT-I analysis set.

Results will be presented in Statistical Table 14.2.2.1.1.

Sensitivity analysis will be performed using alternative definitions of AUC (AUC variant 1 to 3, see Section 6). Results will be presented in Statistical Tables 14.2.2.1.2, 14.2.2.1.3 and 14.2.2.1.4.

Viral load from viral culture will also be described by day relative to treatment baseline assessment and by time point, with a line plot of VL mean values over time (Statistical Table 14.2.2.2 and Figure 14.2.2).

VL-AUC will also be described by quarantine group (main AUC and variant 1 to 3) on the ITT-I set (Statistical Tables 14.2.2.3.1 to 14.2.2.3.4).

Viral load data will be listed in 16.2.6.1.

5.5.2.2 TSS-AUC

The calculation of the Total Symptom Score AUC (TSS-AUC) will be performed on the TSS measured 3 times a Day from the measurement collected at the time of the first dose of IMP to Day 12 (am), using the trapezoidal summation rule based on actual time intervals in hours.
This outcome will be analysed as the primary efficacy endpoint on the ITT-I analysis set. Results will be presented in Statistical Table 14.2.3.1.1.1.

Sensitivity analysis will be performed using alternative definitions of AUC (AUC variant 1 and 2, see Section 6). Results will be presented in Statistical Tables 14.2.3.1.2 and 14.2.3.1.3.

TSS will also be described by day relative to treatment baseline assessment and by time point, with a line plot of TSS values over time (Statistical Table 14.2.3.2.1 and Figure 14.2.4.2.1).

Sensitivity analyses will be performed using the TSS-11 items, with the primary definition of AUC (first dose of IMP to Day 12 am), on ITT-I set (Statistical Tables 14.2.3.1.1.2 and 14.2.3.2.2 and Figure 14.2.4.2.2).

A scatterplot of VL-AUC 10-items vs VL-AUC 11-items will also be produced (Figure 14.2.4.1).

Symptom diary cards data will be listed in 16.2.6.2.

5.5.2.3 VLPEAK

The peak viral load (VLPEAK) is the maximum viral load measured by qRT-PCR or in viral culture in nasal samples, from first assessment after IMP to Day 12 (am).
VLPEAK will be analysed following the same analysis than the primary efficacy endpoint on the ITT-I analysis set.
Results will be presented in Statistical Tables 14.2.4 and 14.2.5.

5.5.2.4 TSSPEAK

The peak Total Symptom Score (TSSPEAK) is the maximum TSS from first assessment after IMP to Day 12 (am).
The analyses will be like the one for Peak VL on the ITT-I analysis set (Statistical Table 14.2.6).

5.5.2.5 Time to VLPEAK

The time from the assessment at the time of the first dose of IMP to VLPEAK in days (see Section 0) will be analysed similarly to the primary efficacy analysis (Statistical Tables 14.2.7 and 14.2.8) on the ITT-I set.

5.5.2.6 Time to TSSPEAK

The time 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 TSSPEAK in days (see Section 6) will be analysed similarly to the primary efficacy analysis (Statistical Table 14.2.9) on the ITT-I set.

5.5.2.7 Time to viral load negativity

The time from the assessment at the time of the first dose of IMP to qRT-viral load negativity and to culture cell viral load negativity in days (see Section 0) will be analyzed using the KaplanMeier method on the ITT-I analysis set. A Kaplan-Meier plot by randomized arm and a KaplanMeier plot by pooled active treatment arm and placebo will be displayed showing the Time to VL negativity. 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 randomized arm and for the pooled active treatment arm (Statistical Tables 14.2.10 and 14.2.11 and Figures 14.2.4.1, 14.2.4.2, 14.2.5.1 and 14.2.5.2).
Log-rank tests between treatment arms will be done for exploratory purpose.

5.5.2.8 Time to first VL negative slope

The time from the assessment at the time of the first dose of IMP to first qRT-PCR VL negative slope and the time to first cell culture VL negative slope in days (see Section 6) will be analysed similarly to the primary efficacy analysis on the ITT-I analysis set (Statistical Tables 14.2.12 and 14.2.13).
This endpoint will be referred to as Time to first VL decline in the tables.

5.5.2.9 Viral load slope after peak

For each participant, the slope between the VLPEAK and the 4 days following VLPEAK will be modelled with a mixed linear model with a random intercept within each participant and time in days from VLPEAK, group and interaction time*group as fixed effects. For group, placebo will be the reference level. An unstructured variance structure will be used. Coefficients and their 95% CIs (t-type confidence interval) will be presented (Statistical Tables 14.2.14 and 14.2.15).
The following SAS code will be used:

```
proc mixed data=dataset method=ml;
class SUBJID TRTPN;
  model AVAL = time TRTPN time* TRTPN / solution CL;
random intercept / subject=SUBJID type=un; run;
```

A plot representing the mean VL curves evolution as estimated with the model since VLPEAK per randomized arm will also be produced (Figures 14.2.7 and 14.2.8).
Participants without any detectable measurements or participants with no assessments after the peak will be excluded from this analysis.
A separate model with pooled active treatment group will also be fit. Details of the computation of time after peak are given in Section 6.

5.5.2.10 Time to resolution from Peak symptom

The time to resolution from peak symptom in days (see Section 6) will be analysed similarly to the primary efficacy analysis on the ITT-I analysis set (Statistical Table 14.2.16).

5.5.2.11 Nasal discharge

Nasal discharge is measured by the total weight of mucus produced and by the total number of tissues used from the day of first dose of IMP up to Day 12 (am).
These parameters will be analysed similarly to the primary efficacy analysis on the ITT-I analysis set (Statistical Tables 14.2.17 and 14.2.18).

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 treatment baseline assessment) and assessment, and treatment group. In order to calculate the time point that each assessment will be presented against, the weight of nasal discharge 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 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 (Figures 14.2.9 and 14.2.10).

Data will be listed in 16.2.6.3.

[redacted]

[redacted]

5.6 Safety analyses

Safety variables will be tabulated and presented for all participants included in the Safety analysis set (SAF) except otherwise specified and subjects will be analysed in their actual treatment arm, except otherwise specified.

5.6.1 Extent of exposure

The total dose, total daily dose received, and exposure duration will also be described using descriptive statistics for quantitative variables (Statistical Table 14.1.13). Results will not be presented for the overall population.
For partial intake of mixed placebo/active treatment, a capsule will be considered to be of 67mg (see Section 3.3.7).
IMP/ Placebo dosing and Challenge virus inoculation information for each participant will be reported respectively in Listings 16.2.5.1 and 16.2.5.2.

5.6.2 Adverse events

5.6.2.1 Adverse event tabulations:

As explained in Section 4.3.1**Error! Reference source not found.**, tabulation of AEs will be done according to three periods based on their date and time of start, as presented in Table 6:

Table 6: periods for AE tabulation

Period	Description	from	to
Period 0	Admission AE	Admission at Day -2 / Day -1	Just before challenge virus inoculation on Day 0
Period 1	Viral Challenge emergent Adverse Events /non treatment Emergent Adverse Events	Challenge virus inoculation on Day 0	Just before first IMP dose between Day 1 and Day 5 (pm)
Period 2	Treatment and Viral Challenge Emergent Adverse Events	First IMP dose between Day 1 and Day 5 (pm)	Actual discharge from the quarantine unit (as scheduled on Day 12 or later on PI's decision)
Period 3	Post quarantine Adverse Events	Actual discharge from the quarantine unit	EOS visit

Tabulation of adverse events will present for each cell the following information: number of participants with at least one occurrence of the event, corresponding percentage and number of events.

The CEAE will be analysed on the Enrolled set while the TEAE will be analysed on the SAF set.

5.6.2.1.1 Summary table of adverse events on the enrolled set (Statistical Table 14.3.1.1):

- Any AE
- Any CEAE whatever the period (i.e., Period 1, 2 or 3)
- Any CEAE during Period 1
- Any CEAE whatever the period (i.e., Period 1, 2 or 3) considered related to the challenge virus (at least possibly related)
- Any CEAE leading to study discontinuation during Period 1
- Any serious adverse events (CESAE) during Period 1
- Adverse events leading to death (if any)

This table will be produced by treatment arm (as treated, participants not treated will be assigned to 'Not treated').

5.6.2.1.2 Summary table of adverse events on the Safety set (Statistical Table 14.3.1.2):

- Any AE
- Any TEAE whatever the period (i.e., period 2 or 3)
- Any TEAE during Period 2
- Any TEAE during Period 3
- Any TEAE whatever the period (i.e., period 2 or 3) considered related to the study treatment (at least possibly related)
- Any TEAE during Period 2 considered related to the study treatment (at least possibly related)
- Any TEAE during Period 3 considered related to the study treatment (at least possibly related)
- Any TEAE during Period 2 leading to study treatment permanent discontinuation (only relevant for Period 2)
- Any TEAE whatever the period (i.e., period 2 or 3) leading to study discontinuation

5.6.2.1.3 Summary table of serious adverse events on the Safety set (Statistical Table 14.3.1.3):

- Any serious adverse events (TESAE) whatever the period (i.e., period 2 or 3)
- Any TESAE during Period 2
- Any TESAE during Period 3
- Any TESAE during Period 2 leading to study treatment permanent discontinuation (only relevant for Period 2).
- Any TESAE leading to study discontinuation, whatever the period (i.e., period 2 or 3)
- Any TESAE considered related to the study treatment, whatever the period (i.e., period 2 or 3)
- Adverse events leading to death (if any)

This table will be produced by treatment arm (as treated).

5.6.2.1.4 Detailed Tables on the safety set:

The following tables will be produced by treatment arm (as treated):

- Any TEAE by SOC and PT whatever the period (i.e., period 2 or 3) (Statistical Table 14.3.2.1)
- Any TEAE by SOC and PT during Period 2 (Statistical Table 14.3.2.2)
- Any TEAE by SOC and PT during Period 3 (Statistical Table 14.3.2.3)

- Any TEAE at least possibly related to IMP by SOC and PT whatever the period (i.e., period 2 or 3) (Statistical Table 14.3.3.1)
- Any TEAE at least possibly related to IMP by SOC and PT during Period 2 (Statistical Table 14.3.3.2)
- Any TEAE at least possibly related to IMP by SOC and PT during Period 3 (Statistical Table 14.3.3.3)
- Any TEAE by SOC, PT and relationship to IMP (Statistical Table 14.3.3.4)

- Any TEAE by SOC/PT and maximum severity whatever the period (i.e., period 2 or 3) (Statistical Table 14.3.4.1)
- Any TEAE by SOC/PT and maximum severity during Period 2 (Statistical Table 14.3.4.2)
- Any TEAE by SOC/PT and maximum severity during Period 3 (Statistical Table 14.3.4.3)

- Any TEAE leading to study treatment permanent discontinuation, by SOC and PT during Period 2 (only relevant for Period 2) (Statistical Table 14.3.5)
- Any TEAE leading to study discontinuation, whatever the period (i.e., period 2 or 3), by SOC and PT (Statistical Table 14.3.6)

- All TESAEs by SOC and PT whatever the period (i.e., period 2 or 3) (Statistical Table 14.3.7.1)

- Any TESAE by SOC and PT during Period 2 (Statistical Table 14.3.7.2)
- Any TESAE by SOC and PT during Period 3 (Statistical Table 14.3.7.3)

5.6.2.1.5 Detailed Tables on the Enrolled set:

- Any CEAE by SOC and PT whatever the period (i.e., Period 1, 2 or 3) (Statistical Table 14.3.8.1)
- Any CEAE by SOC and PT during Period 1 (Statistical Table 14.3.8.2)
- Any CEAE by SOC, PT at least possibly related to the challenge whatever the period (i.e., Period 1, 2 or 3) (Statistical Table 14.3.9.1)
- Any CEAE by SOC, PT and relationship to challenge (14.3.9.2)

- Any CEAE leading to study discontinuation, whatever the period (i.e., Period 1, 2 or 3), by SOC and PT (Statistical Table 14.3.10)
- All serious CESAEs by SOC and PT during Period 1 (Statistical Table 14.3.11)

This table will be produced by treatment arm (as treated, participants not treated will be assigned to 'Not treated').

5.6.2.2 Adverse event listings:

A by-participant AE data listing including participant identifier, onset and resolution dates, relative study days, period, verbatim term, system organ class, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided:

- For Adverse Events in Listing 16.2.7.1
- For Serious Adverse Events in Listing 16.2.7.2
- For treatment related TEAES in Listing 16.2.7.3
- For AEs leading to study discontinuation in Listing 16.2.7.4
- For AEs leading to death (if any) Listing 16.2.7.5
- For challenge emergent AEs Listing 16.2.7.6

5.6.3 Laboratory safety variables

The laboratory data will be directly transferred from the central laboratory to the data management department. Any clinically significant change occurring during the trial must be recorded as an Adverse Event in the CRF.

Laboratory evaluations will be summarized by visit and by treatment arm on the SAF analysis set.

For each biochemistry and haematology variables:

- Quantitative descriptive statistics will be tabulated at each time point over the course of the study (e.g., at each visit) on raw values and change from baseline (Statistical Table 14.3.12.1.1 and 14.3.12.1.2).
- Qualitative descriptive statistics will be tabulated at each time point over the course of the study by clinical significance (normal/abnormal NCS or abnormal CS) (Statistical Table 14.3.12.2.1 and 14.3.12.2.2)

All urinalysis parameters will also be tabulated as qualitative and/or quantitative variables (Statistical table 14.3.12.3)

All laboratory results will be presented in Listings 16.2.8.1.1 to .3 and all clinically relevant abnormality in Listings 16.2.8.2.1 to .3. The following listings will be presented:

Biochemistry

- Biochemistry abnormalities
- Haematology
- Haematology abnormalities
- Urinalysis

In addition, the toxicity grade will be summarised for each laboratory parameter for which toxicity grade criteria are available (See Grading the Severity of Adult and Paediatric Adverse Events, 2017) (Statistical Tables 14.3.12.4.1 to 14.3.12.4.3).

5.6.4 Physical examinations

All individual data for complete and direct physical examination will be provided in Listing 16.2.9.1, and data for clinically significant abnormal results in Listing 16.2.9.2.

5.6.5 Vital signs and tympanic temperature

- Quantitative descriptive statistics will be tabulated by treatment arm for each vital sign recorded (tympanic temperature, heart rate, respiratory rate, systolic and diastolic blood pressure and peripheral arterial oxygen saturation) at each time point over the course of the study (Statistical Table 14.3.13.1).
- Qualitative descriptive statistics will be presented for the entire exam (normal/abnormal NCS or abnormal CS) at each time point over the course of the study by treatment arm (Statistical Table 14.3.13.2).
- All individual measurements will be provided in Listing 16.2.10.1 and 16.2.10.2 for clinically significant abnormalities.

5.6.6 12-Lead Electrocardiogram

- Quantitative descriptive statistics will be tabulated by treatment arm and by pooled active arm for each 12-Lead ECG parameters recorded (Heart rate, QRS, PR interval, QT, QTc) at each time point over the course of the study (Statistical Table 14.3.14.1).
- Qualitative descriptive statistics will be presented for the entire exam (normal/abnormal NCS or abnormal CS) at each time point over the course of the study by treatment arm and by pooled active arm (Statistical Table 14.3.14.2).
- All individual measurements will be provided in Listing 16.2.11.

5.6.7 Spirometry

All individual data for spirometry will be provided in Listing 16.2.12.

5.6.8 Other safety variables

The following data will be presented in listings:

- Nasopharyngeal swab for rapid viral antigen test at discharge from quarantine (Listing 16.2.13)

5.7 Pharmacokinetic Analysis

The PK analysis set will be used for all PK presentations.

5.7.1 Plasma EDP-323 PK Parameters

Plasma PK parameters for EDP-323 and its metabolites will be calculated for the first dose and last dose of EDP-323 by [redacted] 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-323.

Summary statistics for the plasma PK parameters of EDP-323 following administration in healthy adult subjects inoculated with RSV-A Memphis 37b will be tabulated (Statistical table 14.4.1), by actual treatment group, and will also be listed (Listing 16.2.15.1). The summary statistics will include mean, standard deviation, standard error of the mean, coefficient of variation, median, minimum, maximum, geometric mean, geometric standard deviation and geometric coefficient of variation.

The PK parameters to be summarized will include: Cmax, Tmax, t1/2, CLss/F, λz, Vss/F, C12, C24, AUC0-last, tlast, AUC0-tau, and metabolite-to-parent ratio.

Similarly, summary statistics for the plasma PK parameters of EDP-323 metabolites following repeat dose administration in healthy adult subjects inoculated with RSV-A Memphis 37b will be tabulated (Statistical table 14.4.2), by actual treatment group, and will also be listed (Listing 16.2.15.2). The PK parameters for the EDP-323 metabolites to be summarised will include: Cmax, Tmax, t1/2, λz, C12, C24, AUClast, tlast, and AUC0-tau.

Where a PK parameter is flagged [redacted], 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 Tmax, which will be reported with 2 decimals.

5.7.2 Other PK Parameters

The analyses on the other PK aspect will be covered in another SAP, including details on the presentation of PK concentration data and PKPD analysis by [redacted]

6 Derived data

Derived variable	Derivation algorithm

Change from baseline to visit V (continuous)	Change from baseline of variable X: $X\ (Visit\ V) - X(baseline)$ ○ Negative values indicate a decrease in X ○ Positive values indicate an increase in X

Derived variable	Derivation algorithm
GM: Geometric mean (X)	For endpoints that require a geometric mean to be produced, and those endpoints can have raw values of 0 (zero), the GM 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. The value is typically 1 however it may be another small value which is in line with the scale of the data should a value of 1 be unsuitable. $GM(X) = exp\ (\sum_{k=1}^{n} \frac{\log10(\mathrm{X} + \mathrm{constant})}{n} * \ln(10)) - constant$
GMR: Geometric mean ratio (X over Y)	GMR(X/Y) = GM(X) / GM(Y)
GSD: Geometric standard deviation	$GSD(X) = exp(\mathrm{SD}(\log10(\mathrm{X} + \mathrm{constant})) * \ln(10))$
%GCV: geometric coefficient of variation	$\%GCV(X) = \sqrt{exp(SD^2(X))} - 1$
Event Duration (in days)	$(End\ date) - (Start\ date) + 1$
Event Duration (in hours)	$((End\ datetime) - (Start\ datetime))/3600) + 1$
Event Duration (in seconds)	$(End\ datetime) - (Start\ datetime)$+1
Laboratory-confirmed infection	A detailed definition is given in Section 5.3.1.4. In all the document, it will be called laboratory confirmed infection.

Total symptom score	The TSS computation is based on the diary cards that participants complete 3 times per day from Day -1 to Day 11 and once on Day 12. At each assessment, the participants provide scores from 0 to 3 for a list of 11 symptoms (Runny nose, Stuffy nose, Sneezing, Sore throat, Earache, Malaise/tiredness, Headache, Muscle and/or joint ache, Chilliness/Feverishness, Cough and Chest tightness) and scores from 0 to 4 for 2 symptoms (Shortness of breath and Wheeze). An individual TSS is derived at each assessment of the diary card as the sum of the scores given to the 10 following symptoms on that symptom score card, giving a score between 0 and 3: • Runny nose

Derived variable	Derivation algorithm
	• Stuffy nose • Sneezing • Sore throat • Earache • Malaise/Tiredness • Headache • Muscle and/or Joint Ache • Cough • Shortness of breath Handling of missing data for TSS calculations: 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.
Total symptom score – 11-item	As a sensitivity analysis, TSS-11 is derived at each assessment of the diary card as the sum of the scores given to 11 symptoms. In addition to the symptoms used for 10-item TSS, Chilliness/feverishness will also be included. Handling of missing data for TSS-11 calculations: If the subject does not have all 11 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.

Symptom systems

Symptom	System		
	Upper Respiratory	Lower Respiratory	Systemic
Runny nose	X		
Stuffy nose	X		
Sneezing	X		
Sore throat	X		
Earache	X		
Malaise/Tiredness			X
Headache			X
Muscle and/or Joint Ache			X
Chilliness/Feverishness			X
Chest tightness		X	
Cough		X	
Shortness of breath		X	

Derived variable	Derivation algorithm			
	Wheeze		X	

RiiQ	The Respiratory Infection Intensity and Impact Questionnaire is a patient- reported outcome tool. The RiiQ™ records 13-item RSV symptom scores and 3 additional impact scales. The 13-item diary uses a 4-point scale that consists of grading symptoms on the scale of 0 to 3, where Grade 0 is None, Grade 1 is Mild, Grade 2 is Moderate, and Grade 3 is Severe. The 13 RSV symptoms assessed will comprise 3 domains: • LRTD: cough, wheezing, shortness of breath, and coughing up phlegm/sputum; • URTD: nasal congestion and sore throat; • Systemic symptoms: headache, feeling feverish, neck pain, body aches and pain, fatigue/tiredness, interrupted sleep, and loss of appetite. The RiiQ total score and subscores are obtained by summing the corresponding items. They will be referred to as RiiQ total score, RiiQ-L score, RiiQ-U score and RiiQ-S score. The RiiQ™ also consists of 3 additional impact scales that records the impact of RSV disease: • Daily activities on a 4-point scale (0 = No difficulty, 1 = Some difficulty, 2 = Moderate difficulty, 3 = Great difficulty); • Emotions on a 4-point scale (0 = Not at all, 1 = Somewhat, 2 = Moderately, 3 = Extremely); • Social relationships on a 4-point scale (0 = Not at all concerned, 1 = Somewhat concerned, 2 = Moderately concerned, 3 = Extremely concerned). They will be referred to as RiiQ-DA score, RiiQ-E score and RiiQSR score.
Assessment at the time of the first dose of IMP	Assessment at the time of the first dose of IMP is defined as the nearest planned assessment to the first dose of IMP, on the same day. It can be prior to or after dosing. For outcomes measured several times a day, the time between the last assessment before IMP, the first assessment after IMP and the time of IMP will be computed. The assessment at the time of the first dose of IMP will be the one the nearest to the IMP time. For outcomes measured once a day, it will be the assessment the same day than the first dose of IMP.

Derived variable	Derivation algorithm
Area Under the Curve (AUC) of Viral Load and Total Symptom Score (in log10 copies/mL *hour for qRT-PCR VL AUC) (in log10 TCID50/mL*hour for tissue culture VL AUC)	Calculated using the trapezium rule [3]: With n+1 measurements y_i at times t_i, (i = 0,.n), the AUC is calculated as: $$AUC = \frac{1}{2}\sum_{i=0}^{n-1}(t_{i+1} - t_i)(y_i + y_{i+1})$$ The actual time of each assessment will be used in the calculation. Measurements from the time of first IMP to end of quarantine will be used for the computation (for VL AUC, 2 on each day from Day 2 to Day 11 and 1 on Day 12 and for TSS AUC, 3 on each day from Day 1 to Day 11 and 1 on Day 12). Handling of missing data for AUC calculations: The AUC calculation will be based on the available non-missing assessment values between the start and end of the defined AUC time period (Day 1 to Day 12) with the following exceptions: • If the first measurement or the last measurement of the AUC time period is missing, the AUC cannot be adequately calculated as described above. Therefore such cases will be reviewed at the BDRM and decision on if and how to compute the AUC will be taken on a caseby-case basis. For the purposes of VL AUC calculation, if Day 11 VL is not detected, missing Day 12 VL may be imputed to not detected and reviewed by the BDRM. • Even if the formula above can still be calculated, too many missing measurements other than the first or last will impact on the precision of the AUC for the given participant. The participant must have at least 1 nonmissing data recording on each day between the start and end of the defined AUC time period to compute the AUC. • Each specific case will be reviewed during the BDRM and decisions with their rationale documented in the BDRM minutes.

AUC variant 1	For sensitivity analysis, the AUC will also be computed using measurements from the measurement collected at the time of 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.

Derived variable	Derivation algorithm
AUC variant 2	A second sensitivity analysis of AUC will be presented for a fixed time period, which will include data from the first assessment (for VL, Day 2 am and for TSS Day 1 am) through to Day 12.
AUC variant 3	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).
Peak Viral Load or Peak Total Symptom score or Peak RiiQ	Computed as the first maximum observed value for VL (VLPEAK), either measured by qRT-PCR or by quantitative viral culture over first assessment after IMP to Day 12 am, or TSS (TSSPEAK) or RiiQ (one peak per total, subscores or impact scales) over first assessment after IMP to D12 am. Handling of missing data for peak value calculation: In the presence of missing data, the maximum of the available data can still be identified, but it may not correspond to the true peak for the participant, when the peak would have corresponded to one of the missing assessments. Each specific case will be reviewed during the BDRM and decisions to derive a peak value and which value to use, with their rationale documented in the BDRM minutes.

Time (days) to VLPEAK or TSSPEAK or RiiQPEAK	The time to VLPEAK by qRT-PCR or by cell culture is the time from the assessment at the time of the first dose of IMP to VLPEAK. Participants without any detectable measurements in the analysis window will have their peak assign to the time of their last assessment. The time to TSSPEAK is the time from the assessment at the time of the first dose of IMP to TSSPEAK. Participants with TSS=0 during all the analysis window will have their peak assign to their last assessment. The time to RiiQPEAK is the time from the assessment at the time of first IMP to RiiQPEAK (one endpoint is defined per score, subscores and impact scales). Participants with score=0 during all in the analysis window will have their peak assign to their last assessment.
Time (days) to viral load negativity	qRT-PCR (resp. cell culture) viral load negativity is reached at the first time when the viral load is undetectable (<LLOD) by qRT-PCR (resp. by cell culture), after which no further detectable assessment appears. If there are missing values between the last detectable assessment and the first undetectable assessment,

Derived variable	Derivation algorithm
	the missing values will be disregarded and the event will be considered to have happened at the first undetectable assessment. The time to viral load negativity is the time between the time from the assessment at the time of the first dose of IMP and the viral load negativity time. Participants without any detectable measurements in the analysis window will be excluded from this analysis. Participants who do not have a confirmed undetectable (i.e., <LLOD) assessment before Day 12 am, will be censored at their last detectable assessment. Each specific case will be reviewed during the BDRM and decisions to derive a duration and how to derive it, with their rationale documented in the BDRM minutes.

Time (days) to first negative slope	The first negative slope of VL evolution is defined as the timepoint after which there are two consecutive declines in VL. If the first decline goes down to undetectable or unquantifiable, then the next VL should be also undetectable or unquantifiable to meet the definition. Only consecutive planned assessment without missing values will be considered. The time to first negative slope is the time from the assessment at the time of the first dose of IMP to the first negative slope. Participants without any detectable measurements in the analysis window will be excluded from this analysis. Participants who do not have a negative slope during the study (non-decreasing measures) will have the first negative slope imputed at their last measurement. Each specific case will be reviewed during the BDRM and decisions to derive a duration and how to derive it, with their rationale documented in the BDRM minutes.
Time (days) to resolution from peak TSS	The time to resolution from peak TSS is the time between TSSPEAK until the start of the first 24-hour symptom-free (TSS = 0) 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. If there are missing values between the last score higher than zero and the start of the first 24-hour symptom-free period, the

Derived variable	Derivation algorithm
	missing values will be disregarded and the duration will be computed using the first score at 0 as an end date. Each specific case will be reviewed during the BDRM and decisions to derive a duration and how to derive it, with their rationale documented in the BDRM minutes.

Time (days) to retur baseline RiiQ	The time to return to baseline RiiQ is the time from the assessment at the time of IMP to the first RiiQ measurement equal or below baseline value, after which no further increase of score above baseline value is observed. Participants with RiiQ equals or less to baseline during the analysis window will be excluded from these analyses. If there are missing values between the last score higher than baseline and the first value equal or below baseline, the missing values will be disregarded and the duration will be computed using the first score at or lower than baseline as an end date. For RiiQ, one endpoint is defined for each score, subscores or impact scales. Participants who do not return to baseline up to Day 12 am will be censored at their last questionnaire. Each specific case will be reviewed during the BDRM and decisions to derive a duration and how to derive it, with their rationale documented in the BDRM minutes.
Duration of PCR positivity (days)	Duration of positive PCR using a sensitivity-enhanced RSV PCR will use measurements in nasal samples starting on Day 2 up to planned quarantine discharge (Day 12 am). Duration is defined as the time (in days) from first detectable until last detectable (i.e. ≥LLOD) assessment after which no further virus is detected. In case of some non-detectable assessment in-between series of one or more detectable assessments, the last detectable assessment of the last series is to be used as the end of the duration period. If there are missing values between the last detectable assessment and the first undetectable assessment, the missing values will be disregarded and the duration will be computed using the first undetectable assessment as an end date. If at Day 12 the viral load is still detectable and no further measurements are available, the duration will be calculated from the first detectable assessment up to Day 12. This would create some bias. These cases, if any, will be reviewed during the BDRM.

Derived variable	Derivation algorithm

	For subjects with no detectable assessment during the quarantine the duration will be set to 0. Handling of missing qRT PCR results for the derivation of the duration of qRT PCR VL: In the case of one or more missing qRT PCR/viral culture result in between two detectable PCR results, the duration can still be computed. In the case of one or more missing qRT PCR/viral culture measurements at the end of the period, the last one being detectable, the exact timing of the end of the viral shedding is unknown and the exact duration cannot be computed. Each specific case will be reviewed during the BDRM and decisions to derive a duration and how to derive it, with their rationale documented in the BDRM minutes.
Time after VL peak and Time after IMP	For the analysis of the VL slope after peak, the time after peak will be computed in seconds as the difference between the datetime of the assessment of the VL peak and the following assessments. For the analysis of the VL slope between IMP and VL peak, the time after IMP will be computed in seconds as the difference between the datetime of the assessment at the time of IMP and the following assessments. Afterward, the time will be converted in days: $Time_{Days} = \frac{Time_{seconds}}{60 * 60 * 24} = \frac{Time_{seconds}}{86400}$
Febrile illness	Febrile illness is defined in two separate ways, from assessment at the time of IMP up to planned quarantine discharge: 1. Any occurrence of temperature ≥37.9□C 2. A tympanic temperature ≥ 2 standard deviations from baseline, occurring any time from the assessment at the time of the first dose of IMP to Day 12 (Quarantine discharge), where baseline is defined as the mean of the tympanic temperature readings on Days -2 and -1 and pre-challenge on Day 0. The (within subject) standard deviation will be calculated from all tympanic temperature readings used for the baseline calculation shown above.

Upper respiratory tract (URT) Illness	Any one of the following signs and/or symptoms on 2 consecutive scheduled assessments, at least one of which must feature grade 2 severity, or if any of the following attain grade 3
Derived variable	Derivation algorithm
	severity once, from assessment at the time of IMP up to planned quarantine discharge. Note: URT (diary card) symptoms and URT (physical findings – directed and complete physical examinations) signs should not be combined in this algorithm, and should be assessed separately. • Self-reported symptoms: rhinorrhea (runny nose), nasal congestion (stuffy nose), sore throat, sneezing, earache • Physician findings: nasal discharge, otitis, pharyngitis, sinus tenderness
Lower respiratory tract (LRT) Illness	Any one of the following signs and/or symptoms on 2 consecutive scheduled assessments, at least one of which must feature grade 2 severity, or if any of the following attain grade 3 severity once, from assessment at the time of IMP up to planned quarantine discharge. Note: LRT (diary card) symptoms and LRT (physical findings – directed and complete physical examinations) signs should not be combined in this algorithm, and should be assessed separately. • Self-reported symptoms: cough or shortness of breath • Physician findings: New wheezes, rhonchi
Systemic illness	Fulfils the criteria for febrile illness (first definition), or fulfils the definition of URT illness and/or LRT illness, **and** any one of the following symptoms on 2 consecutive scheduled assessments, from assessment at the time of IMP up to planned quarantine discharge, at least one of which must feature grade 2 severity, or if any of the following attain grade 3 severity once: • malaise • headache • muscles and/or joint ache • chilliness • feverishness

7 Interim analysis

No interim analysis is planned.

8 Statistical/Analytical issues

This section systematically reviews the topics listed in Section 11.4.2 of the ICH E3 guidance as important features of the analysis, to ensure none of these topics has been overlooked in the current SAP and to facilitate the writing of the corresponding section in the CSR.

8.1 Adjustments for Covariates

For primary efficacy analysis and some other secondary endpoints, an adjustment on baseline levels is done using an ANCOVA.

8.2 Handling of Dropouts or missing data

Methods for handling missing data are described in Section 5.3.4 and Section 0.

8.3 Interim Analyses and Data Monitoring

No interim analysis is planned for the study. There will be one single final analysis after the database has been locked.

8.4 Multicentre studies

No adjustment on centre will be done.

8.5 Multiple Comparison/Multiplicity

See Section 5.1.2.2: as the study is of exploratory purpose, no adjustment for multiple comparisons / multiplicity of endpoints will be performed. Interpretation of inferential statistical tests will have to take into account the potential risk of type-I error.

8.6 Use of an "Efficacy Subset" of Participants

Several subsets of the ITT efficacy set have been defined: the Intent-to-Treat (ITT) set, the Intent-to-treat Infected (ITT-I) set, the Intent-to-Treat A (ITT-A), the Intent-to-Treat B (ITT-B) and the Per Protocol (PP) set [redacted]. As explained in Section 5.1.2.2, the study is a phase II, proof of concept study, exploratory by nature, aiming at assessing the true biological effect of the IMP used in the best experimental conditions and not the effectiveness of the strategy to treat participants with the IMP in conditions closest to real life, the primary efficacy analysis will be on the ITT-I (infected) analysis set. The other analysis sets will be used for sensitivity analyses.

8.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

8.8 Examination of Subgroups

No specific subgroup analysis will be performed.

9 Change in Analyses Planned

The AE severity grading table has been updated to correspond to the CTCAE grading system.

At Sponsor request, the following changes have been made:

The "time to event after first dosing" has been changed to "the time from the assessment at the time of the first dose of IMP to event". The assessment at the time of the first dose of IMP is the nearest planned assessment to the first dose of IMP.

The main analysis was changed from "t-test or Wilcoxon test" to an ANCOVA adjusted on baseline values. This has been changed as the analysis for nasal discharge, although no inferential statistics were planned per protocol.

The time-to-event endpoints are analysed as duration (i.e., as numeric endpoints, not considering censored data) similarly to the main analysis, apart for the time to VL negativity. Log-rank tests to compare the groups has been added.

The definition of TSS has been clarified. The score is based on 10 items out of the 13 items of the SDC.

The endpoint "Time to return to baseline (last assessment before RSV inoculation) TSS" was changed to "Time to resolution from Peak symptom score".

The definition of LRT illness has been updated. The self-reported symptoms "Chest tightness" and "Wheeze" are no more part of the definition. For URP, earache is added in the definition. A second definition of febrile illness has been added that wasn't defined in the protocol.

URT illness, LRT illness, systemic illness and febrile infection were added as exploratory endpoints. A definition of febrile infection based on deviation from baseline of more than 2 SDs was also added.

Results for pooled active treatment are presented and compared to placebo for efficacy tables.

An analysis of the slope of viral load between IMP and VLPEAK has been added, with associated figures.

10 Software documentation

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

11 Tables, Figures and Listings

This section gives a more detailed description of the safety analysis and representation all planned tables, listings and figures (TLFs) in the study.

11.1 List of tables

n°		Enrolled	ITT	ITT-I	ITT-A	ITT-B	PP	SAF	PK
	Demographics and Baseline characteristics								
14.1.1	Participant disposition	X							
14.1.2.1	Study populations and reasons for exclusion	X							
14.1.2.x	Study populations per quarantine	X							
14.1.3	Protocol deviations	X							
14.1.4.1, .2, .3, .4, .5, .6	Demographic data		X	X	X	X	X	X	
14.1.5	Weight, Height and BMI			X					
14.1.6	Alcohol breath test			X					
14.1.7	Urine drugs of misuse and cotinine screen			X					
14.1.8	Alcohol history			X					
14.1.9	Smoking history			X					
14.1.10	Medical history		X						
14.1.11	Concomitant medications		X						
14.1.12	Compliance to Study intervention		X						
14.1.13	Total dose, Total daily dose and exposure duration							X	
	Efficacy								
14.2.1.1.1.1, .2, .3, .4	Primary efficacy analysis: VL-AUC measured from qRT-PCR			X	X	X	X		
14.2.1.1.2.1, .2, .3, .4	Sensitivity efficacy analysis: VL-AUC variant 1 measured from qRT-PCR			X	X	X	X		
14.2.1.1.3.1, .2, .3, .4	Sensitivity efficacy analysis: VL-AUC variant 2 measured from qRT-PCR			X	X	X	X		
14.2.1.1.4.1, .2, .3, .4	Sensitivity efficacy analysis: VL-AUC variant 3 measured from qRT-PCR			X	X	X	X		
14.2.1.2.1, 2, 3, .4	Primary efficacy analysis: VL measured from qRT-PCR by day and by time point			X	X	X	X		
14.2.1.3.1	Primary efficacy analysis: VL-AUC measured from qRT-PCR by quarantine			X					
14.2.1.3.2	Sensitivity efficacy analysis: VL-AUC variant 1 measured from qRT-PCR by quarantine			X					

14.2.1.3.3	Sensitivity efficacy analysis: VL-AUC variant 2 measured from qRT-PCR by quarantine			X					
14.2.1.3.4	Sensitivity efficacy analysis: VL-AUC variant 3 measured from qRT-PCR by quarantine			X					
14.2.2.1.1	Secondary efficacy analysis: VL-AUC measured from viral culture.			X					
14.2.2.1.2	Sensitivity efficacy analysis: VL-AUC variant 1 measured from viral culture.			X					
14.2.2.1.3	Sensitivity efficacy analysis: VL-AUC variant 2 measured from viral culture.			X					
14.2.2.1.4	Sensitivity efficacy analysis: VL-AUC variant 3 measured from viral culture.			X					
14.2.2.2	Secondary efficacy analysis: VL measured from viral culture by day and by time point			X					
14.2.2.3.1	Secondary efficacy analysis: VL-AUC measured from viral culture by quarantine			X					
14.2.2.3.2	Sensitivity efficacy analysis: VL-AUC variant 1 measured from viral culture by quarantine			X					
14.2.2.3.3	Sensitivity efficacy analysis: VL-AUC variant 2 measured from viral culture by quarantine			X					
14.2.2.3.4	Sensitivity efficacy analysis: VL-AUC variant 3 measured from viral culture by quarantine			X					
14.2.3.1.1.1	Secondary efficacy analysis: TSS-AUC (10-items).			X					
14.2.3.1.1.2	Secondary efficacy analysis: TSS-AUC (11-items).			X					
14.2.3.1.2	Sensitivity efficacy analysis: TSS-AUC (10-items) variant 1.			X					
14.2.3.1.3	Sensitivity efficacy analysis: TSS-AUC (10-items) variant 2.			X					
14.2.3.2.1	Secondary efficacy analysis: TSS (10-items) by day and by time point			X					
14.2.3.2.2	Secondary efficacy analysis: TSS (11-items) by day and by time point			X					
14.2.4	Secondary efficacy analysis: Peak VL measured by qRT-PCR			X					
14.2.5	Secondary efficacy analysis: Peak VL measured by viral culture			X					
14.2.6	Secondary efficacy analysis: Peak TSS (10items)			X					
14.2.7	Secondary efficacy analysis: Analysis of time to VLPEAK measured by qRT-PCR			X					
14.2.8	Secondary efficacy analysis: Analysis of time to VLPEAK measured by cell culture			X					

14.2.9	Secondary efficacy analysis: Analysis of time to TSSPEAK (10-items)			X					
14.2.10	Secondary efficacy analysis: Analysis of time to VL negativity measured by qRT-PCR			X					
14.2.11	Secondary efficacy analysis: Analysis of time to VL negativity measured by cell culture			X					
14.2.12	Secondary efficacy analysis: Analysis of time to first VL decline measured by qRT-PCR			X					
14.2.13	Secondary efficacy analysis: Analysis of time to first VL decline measured by cell culture			X					
14.2.14	Secondary efficacy analysis: Analysis of qRTPCR VL slope after VLPEAK			X					
14.2.15	Secondary efficacy analysis: Analysis of cell culture VL slope after VLPEAK			X					
14.2.16	Secondary efficacy analysis: Analysis of time to resolution from Peak TSS (10-items)			X					
14.2.17	Secondary efficacy analysis: Total weight of mucus produced			X					
14.2.18	Secondary efficacy analysis: Total number of tissues used			X					

[redacted]

	Safety								
	Adverse Events								
14.3.1.1	Summary of Adverse Events on the enrolled set	X							
14.3.1.2	Summary of Adverse Events on the SAF set							X	
14.3.1.3	Summary of Serious Adverse Events							X	
14.3.2.1	Any TEAEs by SOC and PT whatever the period							X	
14.3.2.2	Any TEAEs by SOC and PT during Period 2							X	
14.3.2.3	Any TEAEs by SOC and PT during Period 3							X	
14.3.3.1	Any TEAEs at least possibly related to IMP whatever the period by SOC and PT							X	
14.3.3.2	Any TEAEs at least possibly related to IMP during Period 2 by SOC and PT							X	
14.3.3.3	Any TEAEs at least possibly related to IMP during Period 3 by SOC and PT							X	
14.3.3.4	Any TEAEs by SOC, PT and relationship to IMP							X	
14.3.4.1	Any TEAEs by SOC/PT and maximum severity whatever the period							X	
14.3.4.2	Any TEAEs by SOC/PT and maximum severity during Period 2							X	
14.3.4.3	Any TEAEs by SOC/PT and maximum severity during Period 3							X	
14.3.5	Any TEAEs during Period 2 leading to study treatment permanent discontinuation, by SOC and PT							X	
14.3.6	Any TEAEs leading to study discontinuation, whatever the period, by SOC and PT							X	
14.3.7.1	Any TESAEs by SOC and PT whatever the period							X	
14.3.7.2	Any TESAEs by SOC and PT during Period 2							X	
14.3.7.3	Any TESAEs by SOC and PT during Period 3							X	
14.3.8.1	Any CEAEs by SOC and PT whatever the period	X							
14.3.8.2	Any CEAEs by SOC and PT during Period 1	X							
14.3.9.1	Any CEAEs by SOC, PT at least possibly related to the challenge whatever the period	X							
14.3.9.2	Any CEAEs by SOC, PT and relationship to challenge	X							
14.3.10	Any CEAEs leading to study discontinuation, whatever the period (i.e., Period 1, 2 or 3), by SOC and PT	X							

14.3.11	All serious CESAEs by SOC and PT during Period 1	X							
	Laboratory Safety								
14.3.12.1.1.1	Biochemistry: summary statistics by day							X	
14.3.12.1.1.2	Biochemistry – Change from baseline							X	
14.3.12.1.2.1	Haematology: summary statistics by day							X	
14.3.12.1.2.2	Haematology – Change from baseline							X	
14.3.12.2.1	Biochemistry Results by Normal/Abnormal Categories							X	
14.3.12.2.2	Haematology Results by Normal/Abnormal Categories							X	
14.3.12.3	Urinalysis							X	
14.3.12.4.1	Biochemistry - toxicity grades							X	
14.3.12.4.2	Haematology - toxicity grades							X	
14.3.12.4.3	Urinalysis - toxicity grades.							X	
	Vital Signs and Tympanic Temperature								
14.3.13.1.1	Vital Signs and Tympanic Temperature: summary statistics by day							X	
14.3.1.1.2	Vital Signs and Tympanic Temperature – Change from baseline							X	
14.3.13.2	Vital Signs and Tympanic Temperature: qualitative descriptive statistics							X	
	12-Lead ECG								
14.3.14.1.1	12-Lead ECG: summary statistics by day							X	
14.3.14.1.2	12-Lead ECG – Change from baseline								
14.3.14.2	12-Lead ECG: qualitative descriptive statistics							X	
	Pharmacokinetic analysis								
14.4.1	PK parameters – first dose: quantitative descriptive statistics								X
14.4.2	PK parameters – last dose: quantitative descriptive statistics								X

11.2 List of figures

n°		Enrolled	ITT	ITT-I	ITT-A	ITT-B	PP	SAF
	Efficacy Results							

14.2.1.1, .2, .3, .4	Primary efficacy analysis: Line plot of VL measure by qRT-PCR mean values over time			X	X	X	X	
14.2.2	Secondary efficacy analysis: Line plot of VL measured by viral culture mean values over time			X				
14.2.3.1	Scatterplot of TSS-AUC (10-items) vs TSS-AUC (11-items)			X				
14.2.3.2.1	Secondary efficacy analysis: Line plot of TSS (10-items) mean values over time			X				
14.2.3.2.2	Secondary efficacy analysis: Line plot of TSS (11-items) mean values over time			X				
14.2.4.1	Secondary efficacy analysis: Kaplan-Meier curves for time to VL negativity measured by qRT-PCR			X				
14.2.4.2	Secondary efficacy analysis: Kaplan-Meier curves for time to VL negativity measured by qRT-PCR – Pooled treatment groups			X				
14.2.5.1	Secondary efficacy analysis: Kaplan-Meier curves for time to VL negativity measured by cell culture			X				
14.2.5.2	Secondary efficacy analysis: Kaplan-Meier curves for time to VL negativity measured by cell culture – Pooled treatment group			X				
14.2.6	Secondary efficacy analysis: Slope of qRT-PCR VL load curves from VLPEAK			X				
14.2.7	Secondary efficacy analysis: Slope of cell culture VL load curves from VLPEAK			X				
14.2.8	Secondary efficacy analysis: Line plot of mean weight of mucus produced over time			X				
14.2.9	Secondary efficacy analysis: Line plot of mean number of tissues used over time			X				

[redacted]

Note: Only the Kaplan-Meier figures will be produced by [redacted].

11.3 List of listings

n°	
16.2.1	Subject disposition
16.2.2	Population membership and reason for exclusion
16.2.3	Randomisation list
16.2.4	Protocol deviations

16.2.4	**Demographics and Baseline characteristics data**
16.2.4.1	Demographic characteristics and informed consent
16.2.4.2	Weight, Height and BMI

16.2.4.3	Alcohol breath test
16.2.4.4	Drugs of abuse and Cotinine use
16.2.4.5	Alcohol history
16.2.4.6	Smoking history
16.2.4.7	Urine pregnancy test, serum FSH and β-HCG pregnancy test
16.2.4.8	HIV, Hepatitis B & C and Thyroid function
16.2.4.9	Eligibility criteria
16.2.4.10	Nasal swab respiratory pathogen screen data
16.2.4.11	Medical history
16.2.4.12.1	Medications
16.2.4.12.2	Procedures
16.2.4.13	Visit dates
16.2.5	**Compliance and/or Drug Concentration Data (if available)**
16.2.5.1	IMP/ Placebo dosing
16.2.5.2	Challenge virus Inoculation
16.2.6	**Individual Efficacy Response Data (including derived endpoints)**
16.2.6.1.1	Viral Load Data – qRT-PCR, qic PCR and viral culture
16.2.6.1.2	Viral Load Data – qRT-PCR, qic PCR and viral culture until Day 5
16.2.6.2	Symptom Diary Cards
16.2.6.3	24-hour tissue count & nasal discharge weight
16.2.6.4	Derived efficacy response data
16.2.6.5	Patient perception questionnaire results
16.2.6.6	Dichotomous Virus Infection Outcomes
16.2.6.7	RiiQ
16.2.7	**Safety Data**
	Adverse Events
16.2.7.1	Adverse Events
16.2.7.2	Serious Adverse Events
16.2.7.3	Treatment related TEAES
16.2.7.4	AEs leading to study discontinuation
16.2.7.5	AEs leading to death (if any)
16.2.7.6	Challenge Emergent Adverse Events
	Laboratory Safety Data

16.2.8.1.1	Biochemistry
16.2.8.1.2	Biochemistry – clinically significant abnormalities
16.2.8.2.1	Haematology
16.2.8.2.2	Haematology – clinically significant abnormalities
16.2.8.3.1	Urinalysis
16.2.8.3.2	Urinalysis – clinically significant abnormalities
	Other Safety Data
16.2.9.1	Complete and direct physical examination
16.2.9.2	Complete and direct physical examination – clinically significant abnormalities
16.2.10.1	Vital signs and tympanic temperature
16.2.10.2	Vital signs and tympanic temperature – clinically significant abnormalities
16.2.11	12-Lead Electrocardiogram
16.2.12	Spirometry
16.2.13	Nasopharyngeal swab for rapid viral antigen test at discharge from quarantine
16.2.14	RSV Neutralization Assay
	PK data
16.2.15.1	PK parameters – first dose
16.2.15.2	PK parameters – last dose

12 References

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