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mAbxience Research S.L

MB05-P-01-20 (VH0001 / HVO-CS-001)

A Double-Blind, Randomised, Placebo-Controlled Exploratory Study to Estimate the Prophylactic Efficacy of Palivizumab in Healthy Adult Participants Inoculated with Respiratory Syncytial Virus (RSV)

Version: 3
Date: 03/Dec/2020

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Document version history

Version	Date	Author	Modifications since previous version
V1	05/Oct/2020	Alice Tourneroche	NA for initial release
V2	27/Oct/2020	Alice Tourneroche	• Section 4.2.1.4: Note added for Laboratory-confirmed virus-like-illness definition • Section 6: Precision added for the definition of the subgroup • Section 7.1: Definition of the Infection Rate for Interim Analysis updated to be consistent with the assumptions used in the Sample Size calculation: Variant 2 used instead of Variant 1
V3	03/Dec/2020	Alice Tourneroche	• Section 4.2.1.4: Precision added in URTI, LRTI definition • Section 5.1.2: Normality checks updated • Section 5.3.3: Table number updated • Section 5.4.1: Graphical representation updated • Section 5.4.2.1: ○ Graphical representation updated ○ Graphical representation added for Peak Viral Load (for both qPCR and cell culture) ○ Analysis rule added for Number of days analysis (for both qPCR and cell culture) ○ Analysis rule updated for Time to Peak Virus Shedding analysis • Section 5.4.2.2: ○ Graphical representation updated ○ Graphical representation added for Peak Symptom score ○ Analysis rule added for Number of days analysis Section 11.2: update Figures table according to changes listed above

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Abbreviations and definitions

ADA	Anti-Palivizumab antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BD	Twice Daily
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CK	Creatine Kinase
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CS	Clinically Significant
CSR	Clinical Study Report
CV	Coefficient of variation
DBP	Diastolic Blood Pressure
ELISA	Enzyme-linked Immunosorbent Assay
EWV	Early Withdrawal Visit
ECG	Electrocardiogram
EOS	End Of Study
FEV	Forced Expiratory Volume
FOT	Forced Oscillation Technique
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
FI	Febrile Illness
GAD	Generalised Anxiety Disorder
GP	General Practitioner

[redacted]

HAV	Hepatitis A
HbA1c	Haemoglobin A1c
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HVC	Human Viral Challenge
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IMP	Investigational Medical Product
IV	Intravenous
LLOD	Lower Limit Of Detection
LLOQ	Lower Limits Of Quantification
LRT	Lower Respiratory Tract
LRTI	Lower respiratory tract illness
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCID	Minimal Clinically Important Difference
MCV	Mean Corpuscular Volume
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated measures
NA	Not Applicable
NCS	Non-Clinically Significant
NDA	No Detectable Antibody
NPS	Nasopharyngeal Swab
PCA	Principal Component Analysis
PCR	Polymerase Chain Reaction
PEF	Peak expiratory flow
PFU	Plaque Forming Units
PHQ	Patient Health Questionnaire
PK	Pharmacokinetic
PT	Prothrombin Time

PT	Preferred Term
qRT-PCR	quantitative Reverse Transcriptase-Polymerase Chain Reaction
RBC	Red Blood Cell
RR	Respiratory Rate
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SAF	Safety dataset
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	Systemic Illness
SoA	Schedule of Activities
SOC	System Organ Class
SBP	Systolic Blood Pressure
T	Troponin
TDS	Three Times Daily
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
TSS	Total Symptom Score
ULOQ	Upper Limit Of Quantification
URT	Upper Respiratory Tract
URTI	Upper respiratory tract illness
VL	Viral Load
WBC	White Blood Cell
WHO	Word Health Organization
β-HCG	β-human chorionic gonadotrophin

[redacted]

1 Introduction

This document is the statistical analysis plan (SAP) for the MB05-P-01-20 study. The purpose of this SAP is to provide a comprehensive and detailed description of the statistical analyses that will be carried out to assess the clinical safety, pharmacokinetics/pharmacodynamics, immunogenicity, and efficacy of the study treatment, as outlined in the study protocol version 2 dated 22 May 2020. The SAP pre-specifies the statistical approaches to be used and is validated prior to the study database lock or to any unblinded interim look at the data.

2 Highlights from study protocol

2.1 Background/Rationale

Full details of the background and rationale for the study are provided in Section 1.1.2 of the protocol.

2.2 Study Objectives

2.2.1 Part 1

- Objective 1: To confirm the planned dose of Palivizumab to be given to participants in Part 2
- Objective 2: To assess safety of Palivizumab in healthy adults

2.2.2 Part 2

- Objective 1: To estimate the margin and variance of prophylactic effect of Intravenous (IV) treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo [assessed by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR)].

- Objective 2: To estimate the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo [assessed by cell culture (pfu/mL)].

- Objective 3: To estimate the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo [assessed by total symptom score (TSS) Area-Under-the-Curve (AUC)].

- Objective 4: To estimate the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo [assessed by total symptom score (TSS)].

- Objective 5: To estimate the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo [assessed by total weight of nasal discharge produced and the total number of tissues used in each group].

- Objective 6: To estimate the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo [assessed by viral shedding of RSV-A Memphis 37b in nasal samples, in terms of incidence, duration, and peak].

- Objective 7: To estimate the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo [assessed by symptomatic infection in terms of incidence, duration, and peak symptom score].

- Objective 8: To assess safety of Palivizumab in the RSV human challenge model in healthy adults

- Objective 9: To assess the pharmacokinetics of Palivizumab in the RSV human challenge model in healthy adults

- Objective 10: To assess the Anti-Palivizumab antibody (ADA) in the RSV human challenge model in healthy adults

- Objective 11: To assess lung function in relation to RSV Infection *(optional)*

- Objective 12: To explore the Minimal Clinically Important Difference (MCID) in instrument change *(optional)*

- Objective 13: To explore the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo in relation to baseline immune status. *(optional)*

- Objective 14: To explore the host-pathogen relationship in the RSV human challenge model in healthy adults *(optional)*

2.3 Investigational plan

2.3.1 Study design

This is an exploratory study in healthy adult volunteers aged 18-55 years. The study is formed of two parts, Part 1 (PK sentinel Part), and Part 2 (Viral Challenge Part).

2.3.1.1 Part 1

All participants in part 1 will receive:

- Reference article product
    - Palivizumab (Synagis™)
    - Dose: 8mg/Kg

If there are no safety concerns in Part 1, and PK analysis of Palivizumab treated participants confirms dose level 8mg/Kg to be appropriate, Part 2 will commence with the planned 8mg/Kg treatment dose.

However, if PK analysis of Part 1 suggests that 8mg/kg may be an insufficient dose to provide suitable efficacious coverage in Part 2, then Part 2 will proceed with a dose of 15mg/Kg.

2.3.1.2 Part 2

Participants in Part 2 will be randomised to receive the following on Day -1:

- Reference article product
  - Palivizumab (Synagis™)
  - Dose: either 8mg/Kg or 15mg/Kg (as determined from Part 1)
- Placebo product
  - Sodium Chloride 0.9% Solution (Normal Saline) matched to reference article product

All participants in Part 2 will subsequently receive the following on Day 0:

- RSV challenge virus
  - RSV-A Memphis 37b, total dose of approximately 4.5 log10 plaque forming unit, given intranasally

2.3.2 Determination of sample size

2.3.2.1 Part 1

Approximately 6 participants will be enrolled in Part 1 of the study for an estimated total of 6 evaluable participants. Six evaluable participants are considered sufficient to achieve the objectives of Part 1.

2.3.2.2 Part 2

Approximately 50 participants will be enrolled in Part 2 of the study for an estimated total of 25 evaluable participants per intervention group.

The sample size of 50 challenged and evaluable subjects (25 Palivizumab treated subjects and 25 placebo subjects) in part 2 of the study was calculated based on the assumptions (obtained from the placebo group of prior publications of RSV challenge studies) of an infection rate of 73.7%, a mean area under the viral load-time curve (VL-AUC) of RSV-A Memphis 37b as determined by qRT-PCR on nasal samples in the placebo arm of 20.3 hours*Log10 copies/mL with corresponding SD of 17.8 and CV of 87.9%. Based on these assumptions, and using a 0.05 two-sided type one error probability, the 50 challenged and evaluable subjects will ensure a power of 80% to the detection of a reduction of at least 70% in VL-AUC.
Using a 0.1 two-sided type one error probability, the 50 challenged subjects will ensure a power of 80% to the detection of a reduction between 60 and 65% in VL-AUC.

Reduction in VL-AUC	50%	55%	60%	65%	70%	75%	80%
N/group for 80% power, 5% two-sided	49	40	34	29	25	22	19
Power, 5% two-sided with 25 subjects	0.522	0.601	0.660	0.729	0.800	0.843	0.886
Power, 10 % two sided with 25 subjects	0.644	0.716	0.781	0.835	0.881	0.916	0.940

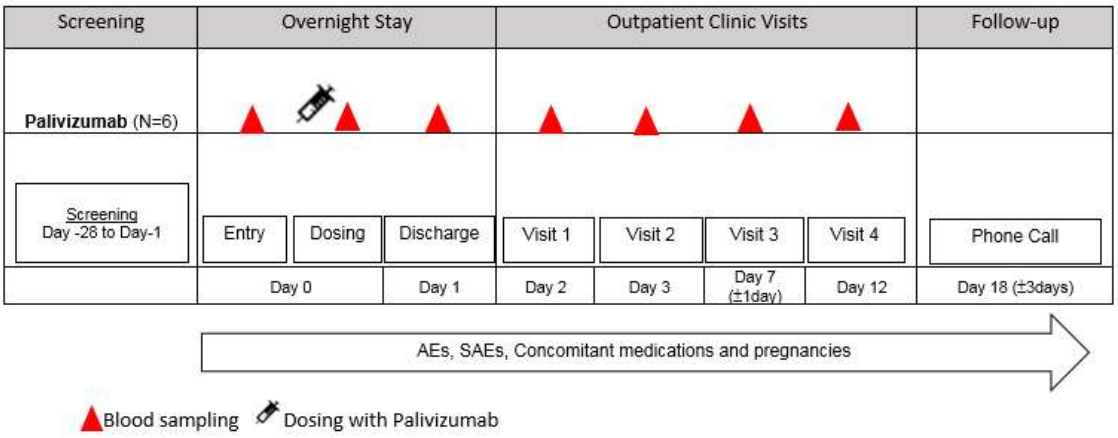
2.3.3 Study assessments and study plan

2.3.3.1 Part 1

The total duration of study participation for a participant is up to approximately 50 days, with the following sequence and duration of study periods:

- **Screening** phase: from Day -28 to Day -1 pre-admission (Historical generic screening data collected through the hVIVO Generic Screening process may be transferred to this study after the study-specific consent form has been signed by the participant)
- **Inpatient phase:** Participants will be resident in the Unit for 1 days (from Day 0 to Day +1). Procedures will include:
    - Admission to Unit on Day 0
    - Study intervention Intravenous (I.V.) dosing on Day 0
    - Post infusion monitoring and PK Day 0 and Day 1
    - Participants will be discharged from the Unit on Day 1 (or may remain longer at the Principal Investigator's discretion)
- **Outpatient phase**: study assessments will be conducted at follow up clinic visits and telephone calls as follows:
    - Clinic visits: Day 2, Day 3, Day 7 (±1 day) and Day12
    - Final safety follow-up by telephone: Day 18 (±3 days).

Part 1



Study Phase ➔	Clinic Screening Phase*	Overnight stay		Clinic visits				Phone call
Study Day ➔ / Procedure ➘	Day -28 to Day -1	Day 0	Day 1	Day 2	Day 3	Day 7(± 1day)	Day 12	Day 18 (± 3 days)
Written consent (a)	X	X						
Eligibility criteria (+)	X	X						
Medical & medication history	X							
Change In medical & medication history		X						
Demographics	X							
Height & weight, BMI (b)	X	X						
Complete physical examination (c)	X	X	X				X	
Vital signs (HR, RR, SBP, DBP, SpO_2)(d)	X	BD	X	X	X	X	X	
Tympanic temperature (d)	X	BD	X	X	X	X	X	
12-lead ECG	X						X	
Spirometry	X							
Urine drugs of abuse screen	X	X						
Urine pregnancy test	X	X					X	
Urinalysis	X						X	
Alcohol breath test		X						
Product Administration								
IMP/Placebo Dosing (e)		X						
Collection of blood samples								
Pharmacokinetic sample (f)		8 X	X	X	X	X	X	
ADA		X				X	X	
HIV, Hepatitis A, B, & C	X							
Haematology (h)	X						X	
Biochemistry (h)	X						X	
Thyroid function test	X							
Serum FSH (post-menopausal women) (i)	X							
Serum β-HCG pregnancy test (all females) (j)	X							
Safety Assessments								
Adverse Events (k)	◄							►
Concomitant medications(k)	◄							►

[redacted]

KEY NOTES FOR PART 1 SCHEDULE OF EVENTS

X	Once
BD	Twice Daily, collected pre and post-dosing.
+	Only the applicable Inclusion/Exclusion criteria will be reviewed at each time point.
*	All screening assessments will be performed under hVIVO Generic Screening process. Results of tests or examinations performed under hVIVO Generic Screening process, and within 28 days prior to study Day 0 may be used to determine eligibility without the need to repeat the assessment following study specific consent.
a	Study specific consent may occur on Day 0, providing all required eligibility information has been collected through hVIVO Generic Screening process.
b	On Day 0, only weight will be measured pre-dosing as individual doses are defined by weight.
c	Day 0 physical examination will be performed pre-dose. Day 1 physical examination will be performed pre-discharge.
d	Vital signs will be measured pre- and post-dose.
e	IV drug delivery (approximately 20minutes infusion).
f	PK blood samples are taken before the start of infusion; at end of infusion, 15mins and 0.5, 1, 4, 8, 12 h; and at 1, 2, 3, 7, 12 days after infusion.
g	ADA blood samples are taken pre infusion and at 7 and 12 days after infusion.
h	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 PI discretion).
i	A serum follicle stimulating hormone (FSH) test will be performed in all post-menopausal women.
i	Blood serum pregnancy test (ß-HCG) will be performed in all female participants who have been tested positive for urine pregnancy testing
k	Adverse events and concomitant mediations are reviewed throughout the study including pre and post dosing with Palivizumab.

[redacted]

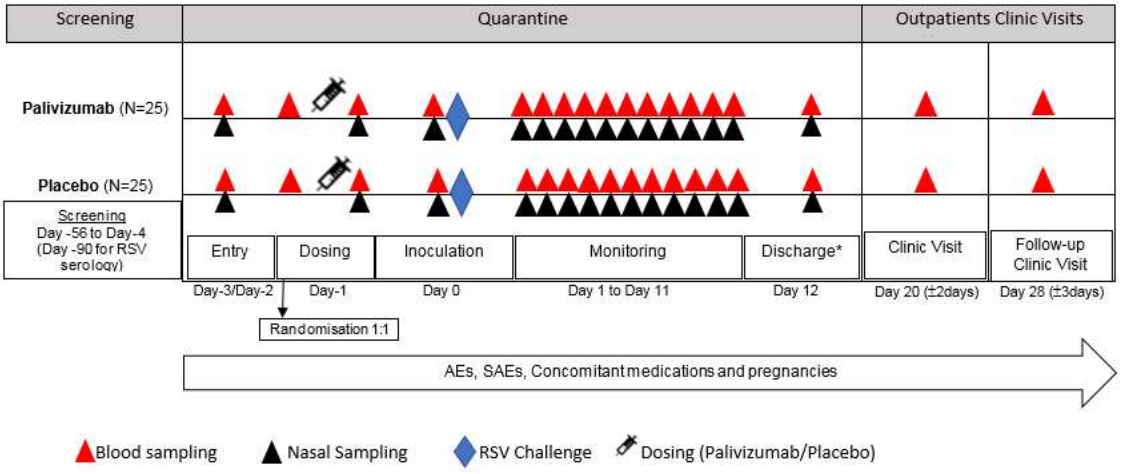
2.3.3.2 Part 2

The total duration of study participation for a participant is up to approximately 122 days, with the following sequence and duration of study periods:

- **Screening** phase: from Day -90 to Day -4 pre-quarantine admission (Historical generic screening data collected through the hVIVO Generic Screening process may be transferred to this study after the study-specific consent form has been signed by the participant)
- **Inpatient phase:** Participants will be resident in the Quarantine Unit for approximately 16 days (from Day -3 to Day 12). Procedures will include:
    - **Pre-human viral challenge (HVC)**:
        - Admission to Quarantine Unit on Day -3
        - Study intervention I.V. dosing on Day -1
    - **HVC**:
        - Challenge Virus inoculation on Day 0
    - **Post-HVC**
        - Day 0 onwards and each day – study assessments will be conducted as per Schedule of Activities
        - Participants will be discharged from the Quarantine Unit on Day 12 (or may remain longer at the Principal Investigator's discretion)
- **Outpatient phase**: study assessments will be conducted
    - Clinic visit for PK sample on Day 20 (±2 days)

Final safety follow-up visit(s): Day 28 (±3 days)

Part 2



*NOTE: Release from quarantine is foreseen at Day 12 in case no virus is detected by PCR (PCR below Ct cut-off) and the participant has no clinically significant symptoms. If the participant continues to have clinically significant symptoms and/or detectable virus on Day 12, additional extended quarantine stay may be required at the discretion of the Investigator

Study Phase	Screening Phase*	QUARANTINE ISOLATION																		Clinic visit		Early withdrawal visit
		Admission to quarantine		Dosing	Human Viral Challenge (HVC)			Post HVC Days											Dis charge			
Study Day	Day -56 to Day -4 (Day -90 for RSV serology)	Day	Day	Day	Day 0			Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day 28 (± 3 days)	
Procedure		-3	-2	-1	Pre	Chall-enge	Post	1	2	3	4	5	6	7	8	9	10	11	12	20 (± 2 days)		
Written consent (m)	X	X																				
Eligibility criteria (+)	X	X[I]		X	X																	
Medical & medication history	X																					
Change In medical& medication history		X[I]																				
Demographics	X																					
Height & weight, BMI (a)	X	X[I]																	(X)		(X)	(X)
Alcohol breath test	X	X[I]																			X	X
Urinalysis	X	X[I]																	X		X	X
Urine drugs of abuse	X	X[I]																			X	X
Urine pregnancy test	X																				X	X
Complete physical examination	X	X[I]		X	X						X			X					X		X	X
Directed physical examination (inc nasal)							X	X	X	X		X	X		X	X	X	X				
Vital signs (HR, RR, SBP, DBP, SpO2 (b)	X	X	TDS	TDS	TDS			TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	X		X	X
Tympanic temperature	X	X	TDS	TDS	TDS			TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	X		X	X
Symptom diary card		X	TDS	TDS	TDS			TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	X			

Study Phase [a]	Screening Phase*	QUARANTINE ISOLATION																		Clinic visit		Early withdrawal visit
		Admission to quarantine		Dosing	Human Viral Challenge (HVC)			Post HVC Days											Dis charge			
24-hour tissue count & nasal discharge weight (c)				X	X			X	X	X	X	X	X	X	X	X	X	X	X			(X)
12-lead ECG	X	X[l]		X[o]							X			X				X			X	X
Spirometry (d)	X	X[l]		X	X			(X)	(X)	(X)	X	(X)	(X)	X	(X)	(X)	(X)	X	X		X	X
PEF (d)			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		X	X
FOT (d)			(X)	(X)	(X)			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)			
Patient Health Questionnaire (PHQ-9)	(X)	(X)[l]																				
Generalised Anxiety Disorder Questionnaire (GAD-7)	(X)	(X)[l]																				
Product Administration																						
Randomisa-tion				X																		
IMP/Placebo Dosing				X																		
Challenge Virus inoculation						X																
Collection of blood samples																						
Pharmacokinetic sample(j)				8 X	X			X	X				X						X	X	X	
Anti-Palivizumab antibody (ADA)(q)				X									X						X		X	
Serum FSH-(post-menopausal women) (e)	X																					
Serum β-HCG pregnancy test (all females) (f)		X[l]																				(X)
HIV, Hepatitis A, B, & C	X																					
Haematology (g)	X	X[l]			X						X			X				X	(X)		X	X
Biochemistry	X	X[l]			X						X			X				X	(X)		X	X
Coagulation	X	X[l]																				X
Cardiac enzymes	X	X[l]									X			X				X				

[redacted] [redacted]

Study Phase	Screening Phase*	QUARANTINE ISOLATION																		Clinic visit		Early withdrawal visit
		Admission to quarantine		Dosing	Human Viral Challenge (HVC)			Post HVC Days											Dis charge			
Thyroid function test	X	(X)[l]																				
Blood sample for serum markers (h)	X	X[l]			X[n]																X	X
Collection of respiratory samples																						
Nasopharyngeal swab / nasal wash - Respiratory pathogen screen (i)	T	X[l]	(X)[n]																			
Nasopharyngeal swab / nasal wash for Rapid viral antigen test or PCR																		X	(X)[n]			(X)
Nasopharyngeal swab / nasal wash Virology (k) & exploratory research	T		X						BD	BD	BD	BD	BD	BD	BD	BD	BD	BD	X			X
Safety Assessments																						
Adverse events (p)	X	←																				X
Concomitant medications (p)	X	←																				X

KEY NOTES FOR PART 2 SCHEDULE OF EVENTS

X	Once
BD	Twice Daily, 12 hours between assessments (± 1 hour).
TDS	Three Times Daily, at the same time each day (± 1 hour).
T	To determine tolerance of the procedure only (sample will not be tested).
+	Only the applicable Inclusion/Exclusion criteria will be reviewed at each time point.

*	All screening assessments will be performed under hVIVO Generic Screening process. Results of tests or examinations performed under hVIVO Generic Screening process, and within 90 days (90 days for viral serology and 56 days for other assessments including safety laboratory test) prior to quarantine admission may be used to determine eligibility without the need to repeat the assessment following study specific consent.
a	Height will be taken at Screening only.
b	Vital signs will be taken at the same time each day (± 1 hour).
c	Distribution of paper issues and bags will start on Day -2, with the first collection on Day -1. Thereafter collection of tissues will occur at the same timepoints (± 1 hour) with tissues distributed 24 h ahead.
d	Assessments will be performed at the same time each day during quarantine (± 1 hour). Where respiratory assessments timepoints occur together, the order of assessments will typically be 1) FOT followed by 2) PEF followed by 3) Spirometry.
e	A serum follicle stimulating hormone (FSH) test will be performed in all post-menopausal women
f	Blood serum pregnancy test (ß-HCG) will be performed in all female participants
g	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 PI discretion).
h	Virus serology (RSV neutralisation antibody assay) will be performed to determine eligibility and seroconversion. *Exploratory RSV-induced immune responses may also be assessed.*
i	Nasopharyngeal swab or nasal wash for respiratory virus screen to assess for the presence of other respiratory viruses; if found positive the participant will not be eligible for the current quarantine. Nasopharyngeal swab or nasal wash for respiratory virus screening includes a Covid-19 test
j	PK blood samples are taken before the start of infusion; at end of infusion, 15mins, and 0.5, 1, 4, 8, and 12 h after infusion; and at 1, 2, 3, 7, 13, 21 and 29 days after infusion.
k	Post inoculation Nasal virology samples will be collected at the same time each day during quarantine (± 1 hour) and used for qRT-PCR and viral culture assay. *Optional exploratory RSV-induced immune responses may also be assessed. Nasal wash is optional under PI discretion, if NPS are being collected BD and used for viral load assessments.*
l	Can be performed on Study Day -3 or Study Day -2.
m	Study specific consent may occur on the day of admission, providing all required eligibility information has been collected through hVIVO Generic Screening process
n	Optional and may be collected or not as per PI discretion for exploratory research
0	Post-dose ECG
p	Adverse events and concomitant mediations are reviewed throughout the study including pre and post dosing with Palivizumab/Placebo and pre and post inoculation.
q	ADA blood samples are taken pre infusion and at 7,13 and 29 days after infusion.
Notes:	Parenthesis indicates the assessment may be optional, or at the PI's discretion. For all participants TDS assessments will commence on Day 0, the first assessment will be pre-virus challenge. The PI 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.

[redacted]

3 Analysis datasets

3.1 Reasons for excluding subjects from analysis datasets

The final selection of subjects for the analysis populations will be discussed in the Data Review Meeting (DRM). Reasons for exclusion of subjects from analysis sets will be documented in the DRM minutes.

3.2 Study discontinuations

3.2.1 Participant Withdrawal

A participant may withdraw their consent to participate in the study at any time, for any reason, without prejudice to his/her future medical care. Participants may decline to give a reason for their withdrawal. Additionally, the PI may withdraw a participant if, in their clinical judgement, it is in the best interest of the participant or if the participant cannot comply with the protocol. Wherever possible, the tests and evaluations listed for the Early Withdrawal Visit (EWV) should be carried out, and if clinically indicated, the participant should be invited back for a final follow up visit. If a participant withdraws from the study during the quarantine phase, an EWV will be completed on the day where possible prior to the participant leaving the unit. It is likely that some of the assessments required as part of the EWV will already have been performed for the study day as per SOA, in this case the completed assessments will not be repeated on the same day unless clinically indicated.
The sponsor should be notified of all study withdrawals in a timely manner, and in cases where the withdrawal is due to a medical reason the participant would be referred to his/her GP.
Participants will be counselled that early withdrawal from the viral challenge phase of the study is strongly discouraged, as it may pose a risk both to the participant and his/her contacts. In the event of a participant insisting on early withdrawal during the challenge isolation period, the participant will be encouraged to stay and would be advised of the potential risks of carrying RSV infection into the community, and to vulnerable groups in particular.
If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

3.2.2 Participant Discontinuation

Participants will be withdrawn from study intervention for the reasons listed below. These participants must not receive any additional intervention but should continue to be followed for safety. Additional unscheduled visits may be performed for safety reasons.

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

[redacted]

- Any intervention related SAEs.
- Anaphylactic reaction following dosing.
- The participant becomes pregnant (if pregnancy is specified as an exclusion criterion).

Participants who are withdrawn from the study, will be requested to attend an Early Withdrawal Visit, with assessments as detailed in the SoA.

3.2.3 Temporary Discontinuation/Temporary Delay in Enrolment

At the first study visit, if a participant is found to be ineligible due to transient circumstances (such as acute disease and/or fever), dosing with Palivizumab will be postponed until transient circumstances have been resolved and the participant will be re-invited to a later quarantine group within the allowed time window.

3.2.4 Participant Replacement Strategy

Participants who withdraw or are discontinued from the study may be replaced in order to achieve the planned evaluable number of participants as follows, if deemed appropriate by the PI and with the approval of the Sponsor:

- In Part 1, withdrawals or early discontinuation prior to the completion of all scheduled clinic visits up to and including Day 12 Visit may be replaced.
- In Part 2, participants who have been dosed but not inoculated may be replaced. The replacement participant will be assigned to the same group as the original (discontinued) participant.
  Participants who have been dosed and inoculated but did not complete the study may be replaced.

3.3 Analysis dataset definitions

3.3.1 Part 1

3.3.1.1 Enrolled

All participants who signed the informed consent.

3.3.1.2 Evaluable

All participants assigned to study intervention and who take a dose of study treatment and who complete visit Day 12 except those participants with protocol deviations that lead to exclusion.

3.3.1.3 Safety Analysis Set (SAF)

All participants assigned to study intervention and who take a dose of study treatment.

3.3.1.4 PK Analysis Set

The PK Analysis set is defined as all participants with at least one postdose PK result.

3.3.2 Part 2

3.3.2.1 Enrolled

All participants who signed the informed consent and randomised to study treatment.

3.3.2.2 Evaluable

All participants randomly assigned to study intervention and who take a dose of study treatment, are given viral challenge, and who complete quarantine. Except those participants with protocol deviations that lead to exclusion.

3.3.2.3 Safety Analysis Set (SAF)

All participants randomly assigned to study intervention and who take a dose of study intervention, regardless of whether they received the challenge virus or not. Participants will be analysed according to the intervention they actually received.

3.3.2.4 PK Analysis Set

The PK Analysis set is defined as all participants with at least one post-dose PK result.

3.3.2.5 Protocol deviations

All deviations will be reviewed and adjudicated as either major with potential impact on efficacy evaluation, major deviations without impact on efficacy evaluation or minor deviations during the blind review meeting, before database lock and code break.

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

- non compliance with the inclusion or non inclusion criteria
- non compliance with the randomisation procedure
- non compliance with study treatment
- non compliance with challenge virus inoculation
- no post-baseline data for the primary efficacy endpoint
- intake of forbidden medication

All other deviations will a priori be considered as minor deviations.

4 Endpoints/Variables/Assessments for analysis

4.1 Part 1

4.1.1 Pharmacokinetic endpoints

- Objective 1:
    - Evaluation of PK levels after intravenous administration of Palivizumab

4.1.2 Safety endpoints

- Objective 2:
  - Frequency and severity of Adverse Events (AEs) and serious AEs (SAEs)
  - Frequency and severity of Treatment Emergent Adverse Events (AEs) and serious AEs (SAEs)
  - Frequency and severity of drug related Treatment Emergent Adverse Events (AEs) and serious AEs (SAEs)

4.2 Part 2

4.2.1 Efficacy endpoints

4.2.1.1 Viral loads/shedding evaluations

- Obective 1:
  - Area under the viral load-time curve (VLAUC) of RSV-A Memphis 37b as determined by qRT-PCR on nasal samples collected twice daily starting two days postviral challenge (Day +2) up to the end of quarantine
- Objective 2:
  - Area under the viral load-time curve (VLAUC) of RSV-A Memphis 37b as determined by cell culture on nasal samples collected twice daily starting two days post-viral challenge (Day +2) up to the end of quarantine.
- Objective 6:
  - Peak
    - Peak viral load of RSV-A Memphis 37b as defined by the maximum viral load determined by quantifiable qRT-PCR measurements in nasal samples starting two days post-viral challenge (Day +2) up to the end of quarantine.
    - Peak viral load of RSV-A Memphis 37b as defined by the maximum viral load determined by quantifiable cell culture measurements in nasal samples starting two days post-viral challenge (Day +2) up to the end of quarantine.
  - Duration
    - Number of days with quantifiable qRT-PCR measurements in nasal samples starting two days post-viral challenge (Day +2) up to the end of quarantine.
    - Number of days with quantifiable cell culture measurements in nasal samples starting two days post-viral challenge (Day +2) up to the end of quarantine.
    - Duration of virus shedding : The time (hours) from first detectable until first confirmed undetectable assessment after their peak measure (after which no further virus is detected).
    - Time to Peak Virus Shedding: The time (days) from inoculation until the peak of virus shedding (qPCR)

4.2.1.2 Symptoms evaluation

- Objective 3:
  - Area under the total symptom score-time curve (TSS-AUC) collected daily in the participant symptom diary card starting one day post-viral challenge (Day +1) up to the end of quarantine.
- Objective 4:

  - Total symptom score sum-time curve (TSS-Sum) collected daily in the participant symptom diary card starting one day post-viral challenge (Day +1) up to the end of quarantine.
- Objective 7:
  - Peak symptom score defined by the maximum daily sum of Symptom score starting one day post-viral challenge (Day +1) up to the end of quarantine.
  - Number of days with symptoms of grade 2 or more, starting one day post-viral challenge (Day +1) up to the end of quarantine.

4.2.1.3 Weight of mucus produced

- Objective 5:
  - Total weight of nasal discharge produced starting one day post-viral challenge (Day +1) up to the end of quarantine.
  - Total number of tissues used by participants starting one day post-viral challenge (Day +1) up to the end of quarantine.

4.2.1.4 Incidence of infection & illness

- Objective 6:
  - Incidence of laboratory-confirmed infection (variant 1 as below)
  - Incidence of laboratory-confirmed infection (variant 2 as below)
- Objective 7:
  - "Laboratory-confirmed virus-like-illness" (variant 3, as below), as defined by:
    - Incidence of "laboratory-confirmed infection", and
    - At least one grade 2 symptom from one or more respiratory categories from the participant symptom diary card
  - "Laboratory-confirmed virus-like-illness" (variant 1, as below)
  - "Laboratory-confirmed virus-like-illness" (variant 2, as below)
  - Upper respiratory tract illness (URTI)
  - Lower respiratory tract illness (LRTI)
  - Systemic illness (SI)
  - Febrile Illness (FI)
  - Fold seroconversion

Laboratory-confirmed infection

"Laboratory-confirmed infection" is defined as the presence of "viral shedding", measured in nasal samples. Subjects with incomplete qPCR data and no recorded data meeting the definition will be treated as not having met the criteria for Laboratory-confirmed RSV infection.

Viral shedding (variant 1)

One or both of the following definitions must be met:

- At least 2 positive quantifiable detections by viral load qPCR assay specific for the challenge virus, reported within 4 consecutive scheduled assessments and from 2 independent samples from Day +2 until discharge (For clarification, see some examples in table below)

Examples of Viral Load qPCR Assay Values (only) and Evidence of Viral Shedding.

Assessment n#	Assessment n+1*	Assessment n+2*	Assessment n+3*	Viral shedding?
Detected	Detected	Detected	Detected	No
1.456	2.359	Any value	Any value	Yes
0.956	Detected	3.647	Any value	Yes
3.452	Not detected	Detected	0.956	Yes
Not Detected	2.359	Not detected	4.852	Yes
Not Detected	1.128	3.647	Not detected	Yes
1.567	Not detected	Not detected	Detected	No
1.5567	Not detected	Not detected	2.434	Yes

qPCR data are scheduled to be collected twice daily (morning and evening).
Assessment n may be on the morning or evening of any given day.
* n+1, n+2 and n+3 are the scheduled assessments following assessment n and independent of study day. For example, Assessment n could be Day 2 evening and Assessment n+3 could be Day 4 morning.

- One positive detection by viral load qPCR assay, specific for the challenge virus, in which an aliquot of the same sample has also tested positive in a viral culture assay appropriate for detecting the challenge virus (i.e. cell-based infectivity assay) from Day +2 until discharge.

For qPCR and the cell-based infectivity assay, a positive detection is any positive numeric or 'Detected' value. A quantifiable detection value is any numeric value and will exclude 'Detected' and 'Not detected' values.

Viral shedding (variant 2)

One or both of the following definitions must be met:

- At least 2 positive detectable assessments by viral load qPCR assay specific for the challenge virus, reported within 4 consecutive scheduled assessments and from 2 independent samples from Day +2 until discharge

- One positive detection by viral load qPCR assay, specific for the challenge virus, in which an aliquot of the same sample has also tested positive in a viral culture assay appropriate for detecting the challenge virus (i.e. cell-based infectivity assay) from Day +2 until discharge.

Laboratory-confirmed virus-like-illness (variant 1)

Virus-like-illness (variant 1) is defined as the occurrence of laboratory-confirmed infection AND any of the following:

- Upper respiratory tract illness (defined below)

[redacted]

- Lower respiratory tract illness (defined below)
- Systemic illness (defined below)
- Febrile illness (defined below).

Laboratory-confirmed virus-like-illness (variant 2)
Virus-like-illness (variant 2) is defined as the occurrence of laboratory-confirmed infection AND symptoms of either of the following:

- any two different self-reported diary card symptoms (≥ Grade 1), or
- at least one Grade 2 self-reported symptom from one or more respiratory categories (URTI and LRTI symptoms defined below).

Laboratory-confirmed virus-like-illness (variant 3)
Incidence of symptomatic RSV infection, as defined by occurence of "laboratory-confirmed infection", AND at least one grade 2 symptom from one or more respiratory categories from the participant symptom diary card

Note: Laboratory-confirmed virus-like-illness definitions will be derived with both Viral shedding definitions.

Upper respiratory tract illness (URTI)
A subject will be considered to have upper respiratory tract illness (URTI) if he/she has any one of thefollowing URT (diary card) self-reported symptom or any one of the following URT (directed physical examination (DPE)) sign on two consecutive scheduled assessments (from the last assessment on Day 0 to quarantine discharge (including any extended quarantine period)), at least one must attain Grade 2 severity, or if any of the following attain Grade 3 severity once. URT (diary card) symptoms and URT (DPE) signs will not be combined in this algorithm and will be assessed and used separately.
Self-reported symptoms (taken from symptom diary card):

- Rhinorrhea (runny nose)
- Nasal congestion (stuffy nose)
- Sore throat
- Sneezing.

Physician findings (taken from DPE):

- Nasal discharge
- Otitis
- Pharyngitis
- Sinus tenderness.

Lower respiratory tract illness (LRTI)
A subject will be considered to have lower respiratory tract illness (LRTI) if he/she has any one of the following LRT (diary card) self-reported symptom or any one of the following LRT (DPE) sign on two consecutive scheduled assessments (from the last assessment on Day 0 to quarantine discharge (including any extended quarantine period)), at least one must attain Grade 2 severity, or if any of the following attain Grade 3 severity once. LRT (diary card) symptoms and LRT (DPE) signs should not be combined in this algorithm and should be assessed separately.
Self-reported symptoms (taken from symptom diary card):

- Cough
- Shortness of breath
- Chest tightness

- Wheezing.

The individual LRT (physicians DPE) signs are:

- New wheezes, rhonchi.

Systemic illness (SI)

A subject will be considered to have SI if he/she fulfils the criteria for any of the following;

- febrile illness (defined below),
- upper respiratory tract illness (defined above)
- lower respiratory tract illness (defined above).

AND

- has any one of the following self-reported symptoms (diary card) on two consecutive scheduled assessments (from the last assessment on Day 0 to quarantine discharge (including any extended quarantine period)), at least one of which must attain grade 2 severity, or if any of the following attain grade 3 severity once:
  - Malaise
  - Headache
  - Muscles and/or joint ache
  - Chilliness / feverishness.

Febrile Illness (FI)

Febrile illness (FI) is defined as a tympanic temperature of ≥ 37.9°C occurring any time from the last assessment on Day 0 to quarantine discharge (including any extended quarantine period)).

Fold seroconversion

Seroconversion is defined as a ≥ 4-fold increase in RSV specific antibodies (measured by RSV Neutralisation Assay) from baseline to follow-up post-quarantine.

Proportion (on any occasion, and on two separate occasions) of subjects with grade 2 or worse symptoms at any day and at each day post-Viral Challenge

Subjects with incomplete data and no recorded symptoms meeting the definition for these endpoints will be treated as not having met the endpoint (i.e. did not experience symptoms of grade 2 or higher).

- *Any Occasion*
  - The proportion of subjects who develop any of the 13 individual symptoms of grade 2 or higher (on any occasion, from the last assessment on Day 0 to quarantine discharge (including any extended quarantine period)) will be calculated. A single occurrence of any of these individual symptoms (of grade 2 or higher) anytime in this period corresponds to meeting the endpoint.
  - In addition, the proportion of subjects who develop any of the 13 individual symptoms of grade 2 or higher, on any occasion for each day separately, will be calculated.
- *Two Separate Occasions*
  - The proportion of subjects who develop any of the 13 individual symptoms of grade 2 or higher (on two separate occasions on any day, from the last assessment on Day 0 to quarantine discharge (including any extended quarantine period)) will be calculated. Two occurrences of any of these individual symptoms (of grade 2 or higher) in this period corresponds to meeting the endpoint.
  - In addition, the proportion of subjects who develop any of the 13 individual symptoms of grade 2 or higher, on any two occasions for each day separately, will be calculated.

Proportion (on any occasion, and on two separate occasions) of subjects with any grade (i.e. grade ≥1) at any day and at each day post-Viral Challenge

Subjects with incomplete data and no recorded symptoms meeting the definition for these endpoints will be treated as not having met the endpoint (i.e. did not experience symptoms of any grade).

- *Any Occasion*
  - The proportion of subjects who develop any of the 13 individual symptoms of any grade i.e. grade ≥1 (on any occasion, from the last assessment on Day 0 to quarantine discharge (including any extended quarantine period)) will be calculated. A single occurrence of any of these individual symptoms of any grade anytime in this period corresponds to meeting the endpoint.
  - In addition, the proportion of subjects who develop any of the 13 individual symptoms of any grade on any occasion for each day separately, will be calculated.
- *Two Separate Occasions*
  - The proportion of subjects who develop any of the 13 individual symptoms of any grade i.e. grade ≥1 (on two separate occasions on any day, from the last assessment on Day 0 to quarantine discharge (including any extended quarantine period)) will be calculated. Two occurrences of any of these individual symptoms (i.e. grade ≥1) in this period corresponds to meeting the endpoint.
  - In addition, the proportion of subjects who develop any of the 13 individual symptoms of any grade i.e. grade ≥1, on any two occasions for each day separately, will be calculated.

4.2.1.5 Temperature

Using the scheduled protocol assessments from the last assessment on Day 0 to quarantine discharge (including any extended quarantine period), this endpoint corresponds to the highest tympanic temperature.

4.2.2 Safety

The safety and tolerability will be evaluated by the monitoring of the occurrence of AEs and SAEs, clinical laboratory results, physical examinations, vital signs, electrocardiogram and concomitant medications.

4.2.2.1 Adverse events

Adverse events (AE) 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).

A 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, i.e. an AE that was not present prior to receiving the first dose of IMP.

Serious adverse events (SAE) are those AE 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)

[redacted]

- 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: to be completed

Tolerability/safety will be assessed over the whole study period.

- Objective 8:
  - Frequency and severity of Adverse Events (AEs) and serious AEs (SAEs)
  - Frequency and severity of Treatment Emergent Adverse Events (AEs) and serious AEs (SAEs)Frequency and severity of drug related Treatment Emergent Adverse Events (AEs) and serious AEs (SAEs)

4.2.2.2 Laboratory endpoints

The following clinical laboratory tests are to be performed on collected blood samples:

- Clinical chemistry: Sodium, Potassium, Glucose (random), Albumin, Chloride, Bicarbonate, Calcium, Uric acid, Total protein, Creatinine, Total, direct, and indirect bilirubin, Inorganic phosphate, Blood urea nitrogen, C-reactive protein (CRP), Gamma glutamyl transferase, Alkaline phosphatase (ALP), Alanine transaminase (ALT), Lactate dehydrogenase (LDH), Aspartate transaminase (AST), Urea
- Hematology: Platelet Count, White blood cell (WBC) count (absolute), WBC differential (Neutrophils, Lymphocyte, Monocytes, Eosinophils, Basophils), Red blood cell (RBC) count, Reticulocyte count (% and absolute), Haemoglobin, Haematocrit, Mean corpuscular volume (MCV), Mean corpuscular haemoglobin (MCH), MCH concentration (MCHC).
- Coagulation: Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT)
- Cardiac enzymes: Creatine Kinase (CK), CK-MB, Troponin (T)Urinalysis: Colour, Specific gravity, Appearance, pH, Presence of blood, glucose, leukocytes, ketones, nitrites, proteins, urobilinogen, bilirubin by dipstick, Microscopy, culture and sensitivity examination (If the dipstick yields abnormal results)

4.2.2.3 Other safety endpoints

4.2.2.3.1 Physical examinations

A complete physical examination to include a full systemic assessment will be performed (General Appearance, Eyes, Ears, Nose, Throat, Head & Neck, Cranial Nerves/ Nervous System, Musculoskeletal Skin, Cardiovascular (heart sounds, pulses), Abdomen/GI system, Respiratory System (breath sounds, resonance, added sounds), Chest – Ausculation (breath sounds, crepitations, wheeze, pleural rub), Chest – Vocal Resonance, Chest – Percussion, Other Findings)

Directed physical examinations will be conducted as deemed appropriate by the Investigator and will include examination of the ears, nose, throat and chest (via stethoscope).
Assessment and grading of any upper respiratory tract (URT) (nasal discharge, otitis, pharyngitis, sinus tenderness) and lower respiratory tract (LRT) symptoms (abnormal breath sounds externally [e.g. stridor] and on chest auscultation [wheezing or rhonchi, crepitations] will be performed. Physician-reported assessments of viral challenge related illness will be graded in accordance with their intensity and documented in the source data.

Safety will be assessed based on abnormalities (normal, abnormal NCS, abnormal CS) for complete examination, and on grades for directed physical examination.

4.2.2.3.2 Vital signs

The following vital signs will be performed:

- Weight (kg), Height (m/cm), BMI
- Heart rate (HR) will be recorded in beats per minute.
- Respiratory rate (RR): respirations will be counted and recorded as breaths per minute.
- BP: systolic BP and diastolic BP will be measured in millimeters of mercury (mmHg); measurements will be made supine.
- Peripheral arterial oxygen saturation (SpO2%) will be assessed using pulse oximetry
  Tympanic temperature (Celsius)

4.2.2.3.3 Electrocardiograms (ECG)

Twelve-lead ECGs will be obtained to evaluate the electrical activity of the heart.

4.2.2.3.4 Concomitant medications

Safety will also be assessed based on the analysis of Concomitant medications coded according to the latest available version of the WHO-Drug dictionary.
"Concomitant" is defined as a medication which was taken during treatment, e.g. stop date later than randomization.
All others will be considered “Prior”.

4.2.2.3.5 ADA

- Objective 10:
  - Anti-Palivizumab antibody (ADA) through Day 28

4.2.3 Pharmacokinetic endpoints

- Objective 9:
  - Palivizumab serum concentrations and serum PK parameters through study Day +28
  - Nasal concentrations (if done) and serum PK parameters through study Day +28

4.2.4 Other endpoints – Tertiary/Exploratory

- Objective 12:
  - Assessments of spirometry, Peak Expiratory Flow (PEF), and Forced Oscillation Technique (FOT)
- Objective 13:
  - The average amount of instrument-assessed change for all participants who rate themselves as "a little better" or "somewhat better”

5 Statistical and Analytical Methods

5.1 General statistical considerations

The statistical analyses are performed in accordance with the ICH E9 guideline.

The statistical analyses will be performed by an external Contract Research Organisation (CRO), Venn Life Sciences, under the responsibility of the Sponsor.

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), CV (Coeffcient Variation), 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 qualitative variables: number of available values, number of missing values, number and percentage of observations in each category of the variable. Except if otherwise specified, percentages will be calculated using the number of available values as denominator (i.e., not including missing values). When relevant, confidence intervals of proportions will be calculated using the Clopper-Pearson exact method (Clopper & Pearson 1934).

All listing will be sorted by treatment group, subject number and time point if applicable.

5.1.2 Significance testing and estimation

When precised in section 5.3, between group comparisons will be performed using appropriate two-sided hypothesis tests at the 5% two-sided significance level.
For normally distributed continuous variables (either raw variable or log-transformed variables) the difference in means, the standard error and the 95% two-sided confidence interval (CI) will be presented. In case of log-transformed variables, in addition to the previous statistics on the log-transformed data, the geometric means and geometric mean ratio and its 95% two-sided CI for the original variable will be presented. The t-test, or Mixed Model for Repeated measures (MMRM) will be used, depending on the endpoint. For endpoints that are not normally distributed (such as total symptom scores), the Wilcoxon Rank-Sum test will be used.
The underlying assumptions of the MMRM presented in Section 5.4.2 will be checked by reviewing the standardized residuals ('Pearson') of the model. If necessary, splines (random coefficient linear regression spline) models will be computed and their fit compared with the fit of the linear model using AICs to address potential departure from linearity.
The underlying assumptions of the t-test will be checked by reviewing the distribution graphically and by reviewing the skewness, the kurtosis and the Shapiro-Wilks test.
For categorical variables, differences in absolute frequency and/or relative risks will be presented, with their 95% two-sided CIs will be presented. Except otherwise specified, the Chi-square test will be used to compare frequencies between groups.
P-values between 0.05 and 0.10 will be considered as indicative of a trend.
As the study is explorative by nature, there will be no attempt to adjust for the multiplicity of endpoints.

5.2 Data handling conventions

5.2.1 Definitions

5.2.1.1 Baseline

Baseline is defined as the last non-missing measurement before dosing. This will usually correspond to the measurement performed at Day-1 before first-dose, unless overruled after review of data at the DRM or otherwise stated in the appropriate endpoint section(s) below, whatever the reason for that assessment (e.g. if it is a repeat assessment, then it should be used as the baseline). However, in case of missing value at Day-1 the last available value recorded during previous visits will be used as baseline value.
If all pre-dose measurements are missing then baseline will be considered as missing, and no changes from baseline and no percentage reduction from baseline will be computed.

5.2.1.2 Quarantine discharge

Unless otherwise specified, Quarantine Discharge refers to actual quarantine discharge regardless of whether discharge from quarantine occurred as scheduled on Day 12, or whether the subject entered an extended quarantine period.

5.2.2 Retest, Outliers

5.2.2.1 Retests

The retests will be managed as follow:

- Any retest before baseline: the last available value before baseline will be used as the baseline
- Any other retest: no value will be used except if otherwise specified during the data review meeting.

5.2.2.2 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.

5.2.3 Missing data and analysis rules

5.2.3.1 Missing data

Missing or incomplete dates:

- For calculation / sorting / assignation based on dates (e.g., treatment emergent AEs, concomitant medications…), the following rules will apply:
- The most conservative approach will be considered (i.e., if the onset date of an AE/concomitant medication is missing / incomplete, it will be assumed to have occurred during the study treatment phase (i.e., a TEAE for AEs) except when the partial onset date or other available data indicates differently (e.g., start date day missing, but month before the month of baseline date, or stop date before baseline date).
- Medical history or disease diagnosis with missing/incomplete date will be assumed to have occurred before any study treatment except when the partial onset date or other available data indicates differently.

- Assignations based on dates will be reviewed and confirmed or infirmed during the data review meeting
- Missing or partial start or end dates of IMP administration, if any, will be reviewed during the data review meeting.

- No other missing data will be imputed except if otherwise specified in Section 4, Section 5.3to 5.6.

5.2.3.2 Analysis rules

Analysis	Associated Units	Assay LLOD	Assay LLOQ	Result	Reported results	Analysis value
RSV titre (qRT-PCR)	Log10 Copies/mL	NA	2.8*	Quantifiable Titre	Value	Reported value
				DETECTED	DETECTED	LLOQ/2
				NOT DETECTED	NOT DETECTED	0
				INVALID	INVALID	Missing data point
				NOT TESTED	NOT TESTED	Missing data point
RSV titre (Plaque assay)	Log10 PFU/mL		1.7	Quantifiable Titre	Value	Reported value
				>6.04	>6.04	6.04 (ULOQ)
				DETECTED	DETECTED	LLOQ/2
				NOT DETECTED	NOT DETECTED	0
				INVALID	INVALID	Missing data point
				NOT TESTED	NOT TESTED	Missing data point
RSV antibody titre	NAb	10	156	NDA	NDA	LLOD
				>=10 and <156	<156	LLOQ/2
				Quantifiable Titre	Value	Reported value
				≥4209	≥4209	4209 (ULOQ)
				INVALID	INVALID	Missing data point
				NOT TESTED	NOT TESTED	Missing data point

*The LLOQ is defined as a cycle threshold (Ct) value of 33.9. This equated to 2.8 Log10 copies/mL by utilisation of a target specific copy number standard curve included in each assay run of the assay validation.
NA: Not Applicable
NDA: No Detectable Antibody
PFU: Plaque Forming Units

5.2.4 Windows for time points

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

5.2.5 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 analysed excpet if otherwise specified during data-review meeting. All data will be presented in the individual data listings and any relevant safety data will be described in the CSR.

5.3 Planned analysis

- **Part 1:**
  - PK analysis will be described in the separate PK analysis plan
  - Safety data will be reviewed during a Safety Data Review Meeting between the Sponsor and the investigator. The following safety data will be reviewed: Vital Signs (heart rate, blood pressure, respiratory rate, and pulse oximetry), Tympanic temperature, Physical examination, Safety laboratory values, Urinalysis, Adverse events, Serious Adverse events and Concomitant medication use.
- **Part 2:**
  - All statistical analysis are described below.
  - The list of statistical Tables, Figures and Listings are provided in Section 11.
  - Efficacy analysis will be on the evaluable population. The safety evaluation will be performed on the SAF population.

5.3.1 Subject disposition and study discontinuations

Subject disposition will be described using a table (Statistical table 14.1.1). The following variables will be tabulated:

- Number of enrolled patients
- Number of randomized subjects
- Number of randomized subjects per treatment group

Study populations will be tabulated, total and per treatment group (Statistical table 14.1.2.1) along with reasons for exclusion from the Evaluable, SAF and PK analysis populations (Statistical tables 14.1.2.2, 14.1.2.3 and 14.1.2.4 respectively).

Study duration and premature study discontinuation will be summarized using the following variables (Statistical table 14.1.3) on SAF population:

- Number of subjects who completed/discontinued the study, total and per treatment group
- Reason of study discontinuation, total and per treatment group
- Study duration, total and per treatment group

All reason for study discontinuation will also be presented in the Listing 16.2.1 along with end of study information.
Visit dates (including date of consent) will be presented in Listing 16.2.4.13.
Population membership and reason for exclusion will be also provided in Listing 16.2.3.

5.3.2 Protocol deviations

All major and minor protocol deviations classified during the data-review meeting will be described in Statistical table 14.1.4 on SAF population and also be provided in Listing 16.2.2.

5.3.3 Demographics and baseline characteristics

The following demographics variables will be summarized by treatment group on the Evaluable and SAF populations (Statistical table 14.1.5 and Listing 16.2.4.1):

- Gender
- Age
- Ethnicity

The following baseline characteristics will be summarized by treatment group on SAF population:

- Weight, Height and BMI (Statistical table 14.1.6 and Listing 16.2.4.2)
- Alcohol breath test (Statistical table 14.1.7 and Listing 16.2.4.3)
- Urine drugs of abuse (Statistical table 14.1.8 and Listing 16.2.4.4)
- Urine pregnancy test (Statistical table 14.1.9 and Listing 16.2.4.5)
- Patient Health Questionnaire (PHQ-9) (Statistical table 14.1.10 and Listing 16.2.4.6)
- Generalised Anxiety Disorder Questionnaire (GAD-7) (Statistical table 14.1.11 and Listing 16.2.4.7)
- HIV, Hepatitis A, B & C (Statistical table 14.1.12 and Listing 16.2.4.8)
- Thyroid function test (Statistical table 14.1.13 and Listing 16.2.4.9)

Eligibility criteria, randomisation information will be presented respectively in Listings 16.2.4.10 and 16.2.4.11)
Nasopharyngeal swab / nasal swab respiratory Pathogen Screen data (including COVID-19 test) will be presented in listing 16.2.4.14.

5.3.4 Medical history – Previous medications

Medical history will be presented by SOC & PT by treatment group (Statistical table 14.1.14).
Previous medications will be presented by ATC code and Preferred Name by treatment group (Statistical table 14.1.15)
Medical history for each subject will be reported in Listings 16.2.4.12.

5.4 Efficacy analyses

5.4.1 Primary efficacy analysis

Objective 1:
To estimate the margin and variance of prophylactic effect of Intravenous (IV) treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy

adults compared to Placebo [assessed by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR)].

Area under the viral load-time curve (VL-AUC) of RSV-A Memphis 37b as determined by **qRT-PCR** on nasal samples collected twice daily starting two days post-viral challenge (Day +2) up to the end of quarantine will be calculated (using the trapezium rule) and tabulated per treatment group. Treatment groups will be compared using t-test if assumptions are valid (Statistical Table 14.2.1.1). In case of distribution not normal, a data transformation could be used.

qRT-PCR will be also tabulated per visit/timepoint for each treatment group (Statistical Table 14.2.1.2).

Spaghetti plots and mean value over time will be used for graphical presentation of qRT-PCR, boxplot will be used for AUC presentation (Statistical Figures 14.2.1.1 to 14.2.1.3).

Individual data for qRT-PCR (included derived data) will be presented on Listing 16.2.6.1.

5.4.2 Secondary efficacy analyses

5.4.2.1 Viral loads/shedding evaluations

a) <u>Objective 2:</u>

To estimate the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo [assessed by cell culture (pfu/mL)].

Area under the viral load-time curve (VL-AUC) of RSV-A Memphis 37b as determined by **cell culture** on nasal samples collected twice daily starting two days post-viral challenge (Day +2) up to the end of quarantine will be calculated (using the trapezium rule) and tabulated per treatment group. Treatment groups will be compared using t-test if assumptions are valid (Statistical Table 14.2.2.1). In case of distribution not normal, a data transformation could be used.

Cell culture will be also tabulated per visit/timepoint for each treatment group (Statistical Table 14.2.2.2).
Spaghetti plots and mean value over time will be used for graphical presentation of cell culture, boxplot will be used for AUC presentation (Statistical Figures 14.2.2.1 to 14.2.2.3).

Individual data for cell culture (included derived data) will be presented on Listing 16.2.6.2.

b) <u>Objective 6</u>

Peak viral load of RSV-A Memphis 37b as defined by the maximum viral load determined by quantifiable qRT PCR measurements in nasal samples starting two days post viral challenge (Day +2) up to the end of quarantine will be calculated and presented by treatment group and compared using t-test if assumptions are valid (Statistical Table 14.2.3.1). In case of distribution not normal, a data transformation could be used.
Peak viral load of RSV-A Memphis 37b will be also described graphically using boxplot (Statistical Figure 14.2.1.4).

Peak viral load of RSV-A Memphis 37b as defined by the maximum viral load determined by quantifiable cell culture measurements in nasal samples starting two days post viral challenge (Day +2) up to the end of quarantine will be calculated and presented by treatment group and compared using test test if assumptions are valid (Statistical Table 14.2.3.2).
Peak viral load of RSV-A Memphis 37b will be also described graphically using boxplot (Statistical Figure 14.2.2.4).

Number of days with quantifiable qRT PCR measurements in nasal samples starting two days post viral challenge (Day +2) up to the end of quarantine will be calculated and presented by treatment group and compared using t-test if assumptions are valid (Statistical Table 14.2.4.1). In case of distribution not normal, a data transformation could be used. In case of missing data on at least one visit, the number of days will be considered as missing for the subject, except if quantifiable measurement is already recorded on other timepoint for this visit..

Number of days with quantifiable cell culture measurements in nasal samples starting two days post viral challenge (Day +2) up to the end of quarantine will be calculated and presented by treatment group and compared using t-test if assumptions are valid (Statistical Table 14.2.4.2). In case of distribution not normal, a data transformation could be used. In case of missing data on at least one visit, the number of days will be considered as missing for the subject, except if quantifiable measurement is already recorded on other timepoint for this visit..

Duration of virus shedding will be analysed using Kaplan-Meier method. A Kaplan-Meier plot by treatment group will be displayed showing the duration of virus shedding (with the time axis as days since first virus shedding). A table will accompany the plot and will display the Kaplan-Meier estimates of the cumulative proportion of subjects' event free at specific time points by treatment group. Subjects who did not have a confirmed undetectable measure after their peak, will be censored at their last detectable assessment. Subjects who do not have a detectable value during quarantine (including any extended quarantine period) will be excluded from the analysis (Statistical Table 14.2.4.3 & Statistical Figure 14.2.3).

Time to Peak Virus Shedding will be described by treatment group. If the peak value is seen on more than one day, the first occurrence is used. Subjects who do not have a detectable value during quarantine (including any extended quarantine period) will be excluded from the analysis. (Statistical Table 14.2.4.4).

5.4.2.2 Symptoms evaluation

a) <u>Objective 3:</u>

To estimate the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo [assessed by total symptom score (TSS)].

A total symptom score will be derived for each subject, separately for each assessment (symptom diary card) on each day, as the sum of the 13 observed symptom grade values for each symptom diary card to obtain a total symptom score for each symptom diary card. If the subject does not have all 13 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.

Area under the total symptom score-time curve (TSS-AUC) collected daily in the participant symptom diary card starting one day post-viral challenge (Day +1) up to the end of quarantine will be calculated (using the trapezium rule) and tabulated per treatment group. Treatment groups will be compared using t-test if assumptions are valid (Statistical Table 14.2.5.1). In case of distribution not normal, a data transformation could be used.

The TSS will be also tabulated per visit/timepoint for each treatment group (Statistical Table 14.2.5.2). Spaghetti plots and mean value over time will be used for graphical presentation of TSS, boxplot will be used for AUC presentation (Statistical Figures 14.1.4.1 to 14.1.4.3).

Following tables will also be displayed:

- Qualitative description for each symptom per visit/timepoint and treatment group (Statistical Table 14.2.5.3)
- Quantitative description (in mm) for each symptom per visit/timepoint and treatment group (Statistical Table 14.2.5.4)

Individual data for Symptom diary cards (included data) will be presented on Listing 16.2.6.3.

b) Objective 4:

To estimate the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo [assessed by total symptom score (TSS)].

Sum Total symptom score-time curve (TSS-Sum) collected daily in the participant symptom diary card starting one day post-viral challenge (Day +1) up to the end of quarantine will be analysed using a MMRM if underlying assumptions valid (Statistical Table 14.2.5.5).

c) Objective 7

Peak symptom score defined by the maximum daily sum of Symptom score starting one day post viral challenge (Day +1) up to the end of quarantine will be determined and tabulated per treatment group. Treatment groups will be compared using t-test if assumptions are valid (Statistical Table 14.2.6.1). In case of distribution not normal, a data transformation could be used.

Peak symptom score will be also described graphically using boxplot (Statistical Figure 14.2.4.4).

Number of days with symptoms of grade 2 or more, starting one day post viral challenge (Day +1) up to the end of quarantine will be calculated and tabulated per treatment group. Treatment groups will be compared using t-test if assumptions are valid (Statistical Table 14.2.6.2). In case of distribution not normal, a data transformation could be used. In case of missing data on at least one visit, the number of days will be considered as missing for the subject, except if grade 2 or more is already recorded on other timepoint for this visit.

5.4.2.3 Weight of mucus produced

a) Objective 5:

To estimate the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared

to Placebo [assessed by total weight of nasal discharge produced and the total number of tissues used in each group].

Total weight of nasal discharge produced and total number of tissues used by participants starting one day post viral challenge (Day +1) up to the end of quarantine will be calculated and tabulated per treatment group. Treatment groups will be compared using t-test if assumptions are valid (Statistical Table 14.2.7.1). In case of distribution not normal, a data transformation could be used.

In addition, weight of nasal discharge produced and number of tissues used by participants will be also tabulated per visit for each treatment group (Statistical Tables 14.2.7.2 and 14.2.7.3 respectively).

Individual data for 24-hour tissue count and nasal discharge weight (included derived data) and will be presented on Listing 16.2.6.4.

5.4.2.4 Incidence of infection & illness

a) Objective 6:

To estimate the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo [assessed by viral shedding of RSV-A Memphis 37b in nasal samples, in terms of incidence, duration, and peak].

Incidence of laboratory-confirmed infection (variant 1) and incidence of laboratory-confirmed infection (variant 2) will be presented by treatment group and compared using chi-square test (Statistical Tables 14.2.8.1 and 14.2.8.2).

b) Objective 7:

To estimate the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo [assessed by symptomatic infection in terms of incidence, duration, and peak].

Incidence of laboratory-confirmed virus-like-illness (Variant 3) will be presented. Treatment group will be compared using chi-square test on both the composite and each component (Statistical Table 14.2.9).

The following infections and illness will be summarised in one Table including data per subject and description by treatment group (Statistical Tbales 14.2.10):

- “Laboratory-confirmed infection” (variant 1)
- “Laboratory-confirmed virus-like-illness” (variant 1)
- “Laboratory-confirmed virus-like-illness” (variant 2)
- Upper respiratory tract illness (URTI)
- Lower respiratory tract illness (LRTI)
- Systemic illness (SI)
- Febrile Illness (FI)
- Fold seroconversion

All Infections data will also be presented in Listing 16.2.6.5.

In addition, the following proportions will be tabulated per treatment group:

- Proportion of Subjects with Grade 2 or higher symptoms on any occasion at any time (Statistical Table 14.2.11.1)
- Proportion of Subjects with Grade 2 or higher Symptoms on any occasion for each day separately (Statistical Table 14.2.11.2)
- Proportion of Subjects with Grade 2 or higher Symptoms on two separate occasions at any time (Statistical Table 14.2.11.3)
- Proportion of Subjects with Grade 2 or higher Symptoms on two separate occasions for each day separately (Statistical Table 14.2.11.4)
- Proportion of Subjects with any symptom (grade >=1) on any cccasion at any time (Statistical Table 14.2.11.5)
- Proportion of Subjects with any symptom (grade >=1) on any occasion for each day separately (Statistical Table 14.2.11.6)
- Proportion of Subjects with any symptom (grade >=1) on two separate occasions at any time (Statistical Table 14.2.11.7)
- Proportion of Subjects with any symptom (grade >=1) on two separate occasions for each day separately (Statistical Table 14.2.11.8)

5.4.2.5 Temperature

The highest tympanic temperature will be calulated and tabulated per treatment group (Statistical Table 14.2.12)

5.4.3 Tertiary/Exploratory efficacy analyses

Tertiary and exploratory objectives are optional and are not included in the list of Tables of this SAP. They might be performed as additional analyses depending on the results of the study.

a) Objective 12:

To explore the Minimal Clinically Important Difference (MCID) in instrument change

The average amount of instrument-assessed change for all participants who rate themselves as "a little better" or "somewhat better" may be presented per treatment group.

b) Objective 13:

To explore the margin and variance of prophylactic effect of IV treatment with Palivizumab administered 1 day prior to inoculation in the RSV human challenge model in healthy adults compared to Placebo in relation to baseline immune status.

The above endpoints may be explored in relation to the baseline status of volunteers and the response to treatment. Baseline status and response can be regarding, but not limited to:

- Immune assays related to Palivizumab (e.g. IgG anti-F ELISA, PCA)
- Baseline immunity to RSV
- Response to Palivizumab treatment

c) Objective 14:

To explore the host-pathogen relationship in the RSV human challenge model in healthy adults .

5.5 Pharmacokinetic (PK) analyses

Objective 1:
To assess the pharmacokinetics of Palivizumab in the RSV human challenge model in healthy adults.

Pharmacokinetic analysis will be described in a separate Clinical Pharmacologyanalysis plan.
Date and time of pharmacokinetic sample will be provided on Listing 16.2.6.6.

5.6 Safety analyses

Safety variables will be tabulated and presented for all subjects included in the SAF population.

5.6.1 Extent of exposure and compliance

IMP/Placebo dosing and Challenge virus inoculation information will be presented respectively in Listings 16.2.5.1 and 16.2.5.2). Compliance, defined as proportion of prescribed study drug actually taken (see section 10) will also be presented in Statistical Table 14.3.9 on evaluable and SAF populations.

5.6.2 Adverse events

Objective 8: To assess safety of Palivizumab in the RSV human challenge model in healthy adults.

Adverse event tabulations:
Tabulation of adverse events will present for each cell the following information: number of subjects with at least one occurrence of the event, corresponding percentage and number of events.
The following tables will be produced by treatment group:

- Summary table of adverse events (Statistical Table 14.3.1.1):
  - Any AE
  - Any TEAE
  - Any TEAE leading to study discontinuation
  - Any TEAE considered related to the study treatment (at least possibly related)
  - Any SAE
  - Any SAE leading to study discontinuation
  - Any SAE considered related to the study treatment
  - Death (if any)

- Detailed Tables:
  - TEAEs by SOC and PT (Statistical Table 14.3.1.2)
  - TEAEs by SOC, PT and severity (Statistical Table 14.3.1.3)
  - At least possibly related TEAEs by SOC, PT and severity (Statistical Table 14.3.1.4)
  - Listing of deaths (Statistical Table 14.3.2)
  - Narrative of deaths, other serious and significant adverse events (Statistical Table 14.3.3)

Adverse event listings:

A by-patient AE data listing including onset and resolution dates, verbatim term, preferred term, blinded treatment, severity, relationship to treatment, action taken, and outcome will be provided in Listing 16.2.7.

5.6.3 Laboratory safety variables

The laboratory values will be directly transferred to the data management department. The laboratory report was interpreted by the investigator. Any clinically relevant changes occurring during the trial were recorded on the AE Form of the CRF.
Laboratory evaluations will be summarized by visit and by treatment group on the SAF population (Statistical tables 14.3.4.1 to 14.3.4.12).
For each hematology, chemistry, coagulation and cardiac enzymes variables:

- Quantitative descriptive statistics will be tabulated at each time over the course of the study (e.g., at each visit) on raw values and change from baseline
- Qualitative descriptive statistics will be tabulated for each laboratory variable at each time over the course of the study by clinical significance (normal, abnormal NCS, abnormal CS) (if relevant)

All urinalysis parameters will also be analyzed as qualitative or quantitative variables per visit (Statistical table 14.3.4.13).

All laboratory results will be presented in Listings 16.2.8.
The following listings will be presented:

- Laboratory reference ranges
- Hematology
- Biochemistry
- Coagulation
- Cardiac enzymes
- Urinalysis

5.6.4 12-Lead Electrocardiogram (ECG)

Quantitative descriptive statistics will be tabulated for each ECG parameters collected [HR (bpm), QRS (ms), PR interval (ms), QT (ms), QTc (ms), QTcF (ms), QTCb (ms), RR (ms)] at each time over the course of the study (e.g., at each visit) on raw values and change from baseline by treatment group. Clinical significance will also be presented for each ECG parameters. (Statistical tables 14.3.5.1 to 14.3.5.3)

In addition, number of patients for the following categories will be displayed for QTcF and QTcB parameters (Statistical Table 14.3.5.4):

- 450 ms
- 480 ms
- 500 ms

- < 30 ms increase from baseline
- [30 ms; 60 ms] increase from baseline
- 60 ms increase from baseline

All individual measurements will be provided in Listing 16.2.9.

5.6.5 Physical examinations

Number of normal, abnormal NCS and abnormal CS values will be presented at each visit by body systems for each treatment group to describe complete physical examination (Statistical Table 14.3.6.1).
Direct physical examination will also be presented. Upper respiratory tract (URT) (nasal discharge, otitis, pharyngitis, sinus tenderness) and lower respiratory tract (LRT) (New Wheezes, Rhonchi) symptoms will be tabulated per visit for each treatment group (Statistical Table 14.3.6.2)
All individual measurements for complete and direc physical examination will be provided respectively in Listings 16.2.10.1 and 16.2.10.2.

5.6.6 Vital signs

- Quantitative descriptive statistics will be tabulated for each vital sign recorded [Heart rate (HR) (beats per minutes), Respiratory rate (RR) (breaths per minutes), Systolic BP (SBP) and Diastolic BP (DBP) (mmHg), Oxygen saturation (SpO2) (%), Tympanic temparature (°C)] at each time over the course of the study (e.g., at each visit) on raw values and change from baseline by treatment group (Statistical tables 14.3.7.1 to 14.3.7.2)
- Qualitative descriptive statistics will be presented for each vital sign at each time over the course of the study (e.g., at each visit) by treatment group: number of subjects with abnormal values beyond clinically important limits (HR<50 or >100 beats per minutes, RR <10 or > 20 breaths per minutes, SBP <90 or >140 mmHg, DBP <50 or >90 mmHg, SpO2 <95%, Tympact temperature <35.5 or >37.8°C) (Statistical table 14.3.7.3)

All individual measurements will be provided in Listing 16.2.11.

5.6.7 Concomitant medications

Concomitant medications will be presented by ATC code and Preferred Name by treatment group (Statistical table 14.3.10)
Previous and concomitant medications for each subject will be reported in Listings 16.2.16.

5.6.8 ADA

Objective 10: To assess the Anti-Palivizumab antibody (ADA) in the RSV human challenge model in healthy adults.

Analyses for ADA results will be described in a separate Clinical Pharmacology analysis plan.
Date and time of samples will be provided on Listing 16.2.6.3.

5.6.9 Other safety variables

Objective 11: To assess lung function in relation to RSV infection.

Spirometry parameters [FEV1 (L), FEV1/FVC (L)], Peak Expiratory Flow (PEF) and Forced Oscillation Technique (FOT) will be presented. Results at each time over the course of the study will be tabulated on raw values and change from baseline by treatment group (Statistical Tables 14.3.8.1 to 14.3.8.6).

Individual data will be provided in Listings 16.2.13 to 16.2.15.

6 Subgroup analysis

A “Laboratory confirmed infected” subgroup will be identified and certain pre-specified analyses will also be performed. Variant 2 of viral shedding will be used for this subgroup.
Analyses expected for this subgroup are identified in section 11.1.

7 Sequence of analysis

7.1 Interim analysis

An interim analysis aiming at reassessing the sample size will be performed once at least 50% of the planned number of challenged participants have been challenged and released from the quarantine unit. This analysis will be performed by the unblinded statistician. This analysis will be solely to confirm the powering assumptions (i.e. infection rate) within the Placebo group and may allow for additional participants to be included into the study, if needed to ensure the study is not underpowered. A second interim look to the placebo infection rate may be conducted when the targeted enrolment is reached, to further consider increasing the sample-size.
Infection rate is defined as the presence of “viral shedding” measured in nasal sample as defined in section 4.2.1.4. Only the first point of the definition variant 2 will be used for the interim analysis to estimate the infection rate.
As the interim look(s) will not compare the two treatment groups on the efficacy endpoints, and as the study is exploratory and statistical testing is not its primary goal, no adjustment to the type I error rate will be made.

7.2 Final analysis

A final analysis will be performed when all endpoint data (safety and efficacy) up to study end (Day 28) are available.
A data-Review meeting (including adjudication of deviations) will be done after Last subject last visit. Data that can unblind the subject will not be reviewed during the data-review (PK, ADA).
The database lock will be done in two steps:

- The first database lock will include all data except those that can unblind the subject and those with a late availability (Plaque assay, PK, ADA data)
- the second database lock will include the remaining data (Plaque assay, PK, ADA data).

Consequently, TFLs will be produced in two steps. One set after each dabase lock.
All available tertiary endpoints available at that time may also be analysed in this step. An integrated CSR containing all data will be written and made available to the sponsor and the Investigator.

7.3 Unblinded statistician

At time of first interim analysis, a statistician from the Venn statistical team will be unblinded. This unblinded statistician will not be involved in any discussions related to data (or SAP modifications) with the remaining blinded team members. The results will be prepared in a separate network working space with specific access rights. Then the interim results will be sent using a ftp site in a dedicated folder for people authorised to have access to unblinded results, secured by specific access rights.

8 Deviations from trial protocol

- The following endpoints have been added:
  - Duration of virus shedding : The time (hours) from first detectable until first confirmed undetectable assessment after their peak measure (after which no further virus is detected).
  - Time to Peak Virus Shedding: The time (days) from inoculation until the peak of virus shedding (qPCR)
  - "Laboratory-confirmed virus-like-illness" (variant 1, as below)
  - "Laboratory-confirmed virus-like-illness" (variant 2, as below)
  - Upper respiratory tract illness (URTI)
  - Lower respiratory tract illness (LRTI)
  - Systemic illness (SI)
  - Febrile Illness (FI)
  - Fold seroconversion
  - Proportion (on any occasion, and on two separate occasions) of subjects with grade 2 or worse symptoms at any day and at each day post-Viral Challenge
  - Proportion (on any occasion, and on two separate occasions) of subjects with any grade (i.e. grade ≥1) at any day and at each day post-Viral Challenge
  - highest tympanic temperature

- The first clause of the viral shedding definition (variant 1) has been revised from the protocol. The new definition puts emphasis on the importance of the number of assessments as opposed to the number of calendar days when confirming the presence of viral shedding. E.g. the SAP definition may span over 3 calendar days but is restricted by 4 consecutive assessments.
  The protocol states:
  "At least two positive "quantifiable" qRT PCR measurements in nasal samples at different timepoints reported within two or more consecutive days starting two days post viral challenge (Day +2) up to the end of quarantine."
  This SAP states:
  "At least 2 positive quantifiable detections by viral load qPCR assay specific for the challenge virus, reported within 4 consecutive scheduled assessments and from 2 independent samples from Day +2 until discharge"

- The first clause of the viral shedding definition (variant 2) has been revised from the protocol. The new definition puts emphasis on the importance of the number of assessments as opposed to the number of calendar days when confirming the presence of viral shedding. E.g. the SAP definition may span over 3 calendar days but is restricted by 4 consecutive assessments.
  The protocol states:
  "At least two positive "detectable" qRT PCR measurements in nasal samples at different timepoints reported within two or more consecutive days starting two days post viral challenge (Day +2) up to the end of quarantine."
  This SAP states:
  "At least 2 positive detectable assessments by viral load qPCR assay specific for the challenge virus, reported within 4 consecutive scheduled assessments and from 2 independent samples from Day +2 until discharge"

- The sequence of analysis has been revised from the protocol.

[redacted]

Initially one main analysis (without Data-Review meeting performed) and one final EOS analysis (after the Data-Review meeting) were planned. This meant that the evaluable population could not be used for the main analysis and led to introducing the "Quarantine completers" population for that analysis. Consequently, the efficacy results could have been slightly different between the Main Analysis and the Final EOS analysis, might the Evaluable population be different from the Quarantine completers, as a result of the data review.
Given that the time between the main analysis (after Day 12) and the final EOS analysis (after Day 28) is very short and due to the delay for avaibility of qRT-PCR data, it is more relevant to perform only one final analysis. In this way, a Data-Review meeting (including review of populations) will be be performed and the Evaluable population can be used to produce the TFLs.

9 Software documentation

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

10 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
Treatment Compliance (continuous)	The compliance Ci for subject i will be computed according to: $$C_i = \frac{D_i^t * 100}{D_i^p}$$ where D_i^p mg is the total amount (mg) of IP prescribed to subject i and D_i^t is the total amount (mg) of IP actually taken by the subject during the study i.e., before the end of study for subject i.
Event Duration	(End Date) – (Start Date) + 1

11 Tables, Figures and Listings

11.1 List of tables

		Enrolled	Evaluable	SAF	Laboratory confirmed infected subgroup
14.1 Demographics and Baseline characteristics					
14.1.1	Subject disposition	X			
14.1.2.1	Study populations	X			
14.1.2.2	Reason for exclusion from the Evaluable set	X			
14.1.2.3	Reason for exclusion from the SAF	X			
14.1.2.4	Reason for exclusion from the PK analysis set	X			
14.1.3	Study duration and premature study discontinuation			X	
14.1.4	Protocol deviations			X	
14.1.5	Demographics data		X	X	
14.1.6	Weight, Height and BMI			X	
14.1.7	Alcohol breath test			X	
14.1.8	Urine drugs of abuse			X	
14.1.9	Urine pregnancy test			X	
14.1.10	Patient Health Questionnaire (PHQ-9)			X	
14.1.11	Generalised Anxiety Disorder Questionnaire (GAD-7)			X	
14.1.12	HIV, Hepatitis A, B & C			X	
14.1.13	Thyroid function test			X	
14.1.14	Medical history			X	
14.1.15	Previous medications			X	
14.2 Efficacy					
14.2.1.1	Primary efficacy analysis - Area under the viral load-time curve (VL-AUC) of RSV-A Memphis 37b as determined by qRT-PCR on nasal samples		X		X
14.2.1.2	qRT-PCR by visit/timepoint		X		X
14.2.2.1	Area under the viral load-time curve (VL-AUC) of RSV-A Memphis 37b as determined by cell culture on nasal samples		X		X
14.2.2.2	Cell culture by visit/timepoint		X		X
14.2.3.1	Peak viral load of RSV-A Memphis 37b - qRT PCR		X		X
14.2.3.2	Peak viral load of RSV-A Memphis 37b - Cell culture		X		X
14.2.4.1	Number of days with quantifiable qRT PCR measurements in nasal samples		X		X
14.2.4.2	Number of days with quantifiable cell culture measurements in nasal samples		X		X

		Enrolled	Evaluable	SAF	Laboratory confirmed infected subgroup
14.2.4.3	Duration of virus shedding		X		
14.2.4.4	Time to Peak Virus Shedding		X		
14.2.5.1	Area under the total symptom score-time curve (TSS-AUC) collected daily in the participant symptom diary card		X		X
14.2.5.2	TSS by visit/timepoint		X		X
14.2.5.3	Symptoms - Qualitative description by visit/timepoint		X		
14.2.5.4	Symptoms - Quantitative description by visit/timepoint		X		
14.2.5.5	Total symptom score - MMRM		X		X
14.2.6.1	Peak symptom score		X		
14.2.6.2	Number of days with symptoms of grade 2 or more		X		X
14.2.7.1	Total weight of nasal discharge produced		X		X
14.2.7.2	Weight of nasal discharge produced by visit		X		
14.2.7.3	Number of tissues used by participants by visit		X		
14.2.8.1	Laboratory-confirmed infection (Variant 1)		X		
14.2.8.2	Laboratory-confirmed infection (Variant 2)		X		
14.2.9	Laboratory-confirmed virus-like-illness (Variant 3)		X		
14.2.10	Incidence of Illness		X		
14.2.11.1	Proportion of Subjects with Grade 2 or Worse Symptoms on Any Occasion at any time		X		
14.2.11.2	Proportion of Subjects with Grade 2 or higher Symptoms on any occasion for each day separately		X		
14.2.11.3	Proportion of Subjects with Grade 2 or higher Symptoms on two separate occasions at any time		X		
14.2.11.4	Proportion of Subjects with Grade 2 or higher Symptoms on two separate occasions for each day separately		X		
14.2.11.5	Proportion of Subjects with any symptom (grade >=1) on any cccasion at any time		X		
14.2.11.6	Proportion of Subjects with any symptom (grade >=1) on any occasion for each day separately		X		
14.2.11.7	Proportion of Subjects with any symptom (grade >=1) on two separate occasions at any time		X		
14.2.11.8	Proportion of Subjects with any symptom (grade >=1) on two separate occasions for each day separately		X		
14.2.11	Highest tympanic temperature		X		
14.3 Safety					
14.3.1.1	Summary table of adverse events			X	X
14.3.1.2	TEAEs by SOC and PT			X	

[redacted]

		Enrolled	Evaluable	SAF	Laboratory confirmed infected subgroup
14.3.1.3	TEAEs by SOC, PT and severity			X	
14.3.1.4	At least possibly related TEAEs by SOC, PT and severity			X	
14.3.2	Listing of deaths			X	
14.3.3	Narrative of deaths, other serious and significant adverse events			X	
14.3.4.1	Hematology - Absolute values			X	
14.3.4.2	Hematology - Change from baseline			X	
14.3.4.3	Hematology - Clinical significance			X	
14.3.4.4	Biochemistry - Absolute values			X	
14.3.4.5	Biochemistry - Change from baseline			X	
14.3.4.6	Biochemistry - Clinical significance			X	
14.3.4.7	Coagulation - Absolute values			X	
14.3.4.8	Coagulation - Change from baseline			X	
14.3.4.9	Coagulation - Clinical significance			X	
14.3.4.10	Cardiac enzymes - Absolute values			X	
14.3.4.11	Cardiac enzymes - Change from baseline			X	
14.3.4.12	Cardiac enzymes - Clinical significance			X	
14.3.4.13	Urinalysis			X	
14.3.5.1	12-lead ECG - Absolutes values			X	
14.3.5.2	12-lead ECG - Change from baseline			X	
14.3.5.3	12-lead ECG - Clinical significance			X	
14.3.5.4	12-lead ECG - Abnormalities			X	
14.3.6.1	Complete physical examination			X	
14.3.6.2	Direct physical examination			X	
14.3.7.1	Vital signs - Absolute values			X	
14.3.7.2	Vital signs - Change from baseline			X	
14.3.7.3	Vital signs - Abnormalities			X	
14.3.8.1	Spirometry - Absolute values			X	
14.3.8.2	Spirometry - Change from baseline			X	
14.3.8.3	Peak Exploratory (PEF) - Absolute values			X	
14.3.8.4	Peak Exploratory (PEF) - Change from baseline			X	
14.3.8.5	Forced Oscillation Technique (FOT) - Absolute values			X	
14.3.8.6	Forced Oscillation Technique (FOT) - Change from baseline			X	
14.3.9	Compliance		X	X	
14.3.11	Concomitant medications			X	

[redacted]

11.2 List of figures

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14.2 Efficacy			
14.2.1.1	qRT-PCR - Spaghetti plots	X	X
14.2.1.2	qRT-PCR - Mean value over time	X	X
14.2.1.3	qRT-PCR - VL-AUC- Boxplot	X	X
14.2.1.4	qRT-PCR - Peak Viral Load - Boxplot	X	X
14.2.2.1	Cell culture - Spaghetti plots	X	X
14.2.2.2	Cell culture - Mean value over time	X	X
14.2.2.3	Cell culture – VL-AUC - Boxplot	X	X
14.2.2.4	Cell culture - Peak Viral Load - Boxplot	X	X
14.2.3	Kaplan-Meier Curve	X	X
14.2.4.1	Total Symptom Score (TSS) - Spaghetti plots	X	X
14.2.4.2	Total Symptom Score (TSS) - Mean value over time	X	X
14.2.4.3	Total Symptom Score (TSS) – AUC - Boxplot	X	X
14.2.4.4	Peak symptom score - Boxplot	X	X

11.3 List of listings

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16.2.3	Population membership and reason for exclusion
16.2.4.1	Demographics data
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16.2.4.3	Alcohol breath test
16.2.4.4	Urine drugs of abuse
16.2.4.5	Urine pregnancy test
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16.2.4.7	Generalised Anxiety Disorder Questionnaire (GAD-7)
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16.2.4.9	Thyroid function test
16.2.4.10	Eligibility criteria
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16.2.5.1	IMP/Placebo dosing
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16.2.6.1	qRT-PCR
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16.2.6.3	Symptom diary cards
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16.2.15	Forced Oscillation Technique (FOT)
16.2.16	Previous and concomitant medications

12 References

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