Protocol Title:	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)
NCT Number:	NCT04540627
Protocol version date:	Version 2.0, 22 May 2020

CLINICAL STUDY PROTOCOL

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)

Short title:	An RSV Human Challenge Study of Palivizumab in Healthy Adult Participants
Version and Date of Protocol:	Final V2.0 _Date 22 May 2020
Sponsor Protocol Number:	MB05-P-01-20
hVIVO Protocol Number:	HVO-CS-001
Sponsor:	**mAbxience Research S.L.** Manuel Pombo Angulo 28, 3rd floor Madrid Spain Postal Code: 28050 Phone: +34 917 711 500
Compound Number:	Palivizumab (Synagis ™)
EudraCT number:	2020-001044-26

Confidentiality and Protections Statement:

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

Personal data included in the protocol is subject to General Data Protection Regulation (GDPR: EU 2016/679) considerations and protections.

Sponsor Statement:

This protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the study intervention, and with the moral, ethical and scientific principles governing clinical research as set out in the current Declaration of Helsinki and the principles of International Council for Harmonisation (ICH) Good Clinical Practice (GCP).

Sponsor Signatory:

[redacted]

[Name] **Date** (DD MMM YYYY)

[Title]

Investigator Agreement:

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

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

Principal Investigator (PI) Signatory:

Name (typed or printed): _____

Institution and Address: [redacted]

Signature: _____ Date: _____

(DD MMM YYYY)

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

From:
Sent:
To:
Cc:
Subject:

[redacted]

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Key Protocol Contributors	Refer to the local study contact list document

Protocol Amendment Summary of Changes Table

PROTOCOL HISTORY		
Document	**Date**	**Amendment Type**
Initial Clinical Trial Protocol (v1.0)	24 Mar 2020	Not applicable. First Version.
Protocol Amendment 01 (v2.0)	22 May 20202	Substantial Amendment

Amendment 01 (22-May-2020)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
7.1 Participant Withdrawal; 1.3.2 Part 2 SOA	Assessments to be performed at the Early Withdrawal Visit (EWV) have been updated to clarify the assessments that should be performed, where possible, and the optional assessments that are performed at the PI's discretion. Section 7.1 updated to incorporate specific text to clarify that, in the scenario where a Participant withdraw from the quarantine phase, EWV assessments will not be repeated for assessments already performed on the day as part of the study SOA unless clinically indicated.	Clarification of the assessments performed at the EWV.
8.14 Nasal Discharge Collection from Paper Tissues; 1.3.2 Part 2 SOA	Section 8.14 updated to clarify that the distribution of paper tissues and bags will start on Day -2, with the first collection on Day -1 as stated in the study protocol SOA. Thereafter distribution and collection of tissues will occur daily until the discharge from quarantine. Part 2 SOA has been revised to resolve the inadvertent inclusion of paper tissues collection on Day 28 Follow-up Visit due to administrative error.	Text revised to resolve an administrative error.
8.20.1.2 Respiratory Pathogen Screen, 1.3.2 Part 2 SOA	Section 8.20.1.2 amended to incorporate specific text confirming that the nasopharyngeal swab or nasal wash collected on entry to quarantine will be tested to detect the presence of a set of respiratory pathogens, including Covid-19, that could potentially contraindicate a participant's participation in the study. Part 2 SOA updated to specify that the nasopharyngeal swab or nasal wash for respiratory pathogen screen can be performed on either Study Day -3 or Study Day-2.	Inclusion of Covid-19 testing as part of the Respiratory Pathogen Screen
6.3. Randomisation and Blinding	Section 6.3 amended to incorporate an update to the process for emergency unblinding. An individual access to a secured website will be provided to the Investigator to replace code break envelopes. Reference to the code break envelopes has been amended throughout the document.	Process for emergency unblinding amended

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1. Protocol Summary

1.1. Synopsis

1.1.1. Indication(s):

Palivizumab is a marketed prophylactic monoclonal antibody (mAb) for the prevention of serious lower respiratory tract disease caused by Respiratory Syncytial Virus (RSV) in children at high risk for RSV disease.

1.1.2. Rationale:

There are currently no effective vaccines to prevent RSV in children, and treatment options for RSV-infected individuals are limited. Palivizumab is licensed for immunoprophylaxis against RSV in young high-risk children, requiring 5 monthly doses and is not affordable in Low to Medium Income Countries (LMICs). The high costs of Palivizumab (US$9600/per season in the USA, and €5000 in Europe) make this biotherapeutic product unaffordable for children in LMICs, which are the areas where the virus is most prevalent and the associated mortality rates are the highest. According to data from The Lancet, between 66,000 and 199,999 children died from complications stemming from RSV in 2005. 99% of those deaths were recorded in developing countries. Therefore, in order to provide effective and affordable RSV immunoprophylaxis for young high-risk children in LMICs, biosimilars for Palivizumab are being developed.

As no data exists for Palivizumab in the RSV human challenge model, this exploratory study is therefore planned to establish the margins of effect and variance of prophylactically administered Palivizumab within the RSV-A Memphis 37b challenge model in healthy adult volunteers. This will enable subsequent evaluation of biosimilars (such as MB05) for prophylactic equivalence or non-inferiority to the reference article (Palivizumab), in the RSV human challenge model.

The study will be performed in adults aged 18-55 years, in two parts.

- Part 1: All participants will be administered Palivizumab (8mg/Kg, intravenously). Pharmacokinetic (PK), safety will be measured.
    - If there are no safety concerns in Part 1, and PK analysis of Palivizumab treated participants confirm the modelling of 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 insufficient dose to provide suitable efficacious coverage in Part 2, then Part 2 will proceed with a dose of 15mg/Kg.
- Part 2: Participants will be either administered Palivizumab (8mg/Kg or 15mg/Kg, as determined in Part 1) or a placebo and they will subsequently be challenged with an RSV-A strain (Memphis 37b). The margin of effect and variance between groups will be measured, as well as safety and reactogenicity.

1.1.3. Objectives and Endpoints:

1.1.3.1. Part 1 Objectives and Endpoints

Objectives	Endpoints
• To confirm the planned dose of Palivizumab to be given to participants in Part 2	• Evaluation of PK levels after intravenous administration of Palivizumab
• To assess safety of Palivizumab in healthy adults	• 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)

1.1.3.2. Part 2 Objectives and Endpoints

Objectives	Endpoints
• 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)].	The margin and variance will be estimated as follows: • 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.
• 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)].	The margin and variance will be estimated as follows: • 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.
• 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)].	The margin and variance will be estimated as follows: • 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.
• 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)].	The margin and variance will be estimated as follows: ○ 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.

Objectives	Endpoints
• 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].	The margin and variance will be estimated as follows: • 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.
• 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].	The margin and variance will be estimated as follows: ○ Occurrence of 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. ○ Occurrence of 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. ○ 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. ○ 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. Similar endpoints may be evaluated based on quantitative viral culture assay.
• 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].	The margin and variance will be estimated as follows: • Incidence of symptomatic RSV infection, as defined by: ○ Incidence of infection, and ○ At least one grade 2 symptom from one or more respiratory categories from the participant symptom diary card. • Number of days with symptoms of grade 2 or more, starting one day post-viral challenge (Day +1) up to the end of quarantine.

Objectives	Endpoints
	• 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.
• To assess safety of Palivizumab in the RSV human challenge model in healthy adults	• 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)
• To assess the pharmacokinetics of Palivizumab in the RSV human challenge model in healthy adults	• Palivizumab serum concentrations and serum PK parameters through study Day +28
• To assess the Anti-Palivizumab antibody (ADA) in the RSV human challenge model in healthy adults	• Anti-Palivizumab antibody (ADA) through Day 28
Tertiary/Exploratory	
• To assess lung function in relation to RSV infection	• Assessments of spirometry, Peak Expiratory Flow (PEF), and Forced Oscillation Technique (FOT)
• 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"
• 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
• To explore the host-pathogen relationship in the RSV human challenge model in healthy adults	• Immune assays related to Palivizumab • RSV baseline immunity and immune responses to infection

*Note that tertiary objectives and endpoints are optional and might be assessed only if needed; therefore, not all testing might be performed and reported.

1.1.4. Overall 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).

1.1.4.1. Part 1 design

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. Refer to Appendix 10.1.5 for details on the Safety Data Review from Part 1.

1.1.4.2. Part 2 design

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 $\log_{10}$ plaque forming unit, given intranasally

The Study Schematic - showing participant progression through the study - is presented in Section 1.2; the Schedules of Activities (SoA) are presented in Section 1.3.

1.1.5. Disclosure Statement:

This is an exploratory study to evaluate the prophylactic efficacy of intravenously administered Palivizumab protecting heathy 18 to 55-year-old adults from RSV infection/disease after RSV inoculation. This study is composed of 2 parts:

- Part 1 is an open label one armed cohort where all participants will receive a single 8mg/kg dose of Palivizumab administered intravenously.
- Part 2 is a double-blinded, two-armed cohort where participants will be randomised to receive Palivizumab (as either a single 8mg/kg or 15mg/kg dose) or Placebo administered intravenously, and subsequently inoculated with RSV-A Memphis 37b.

1.1.6. Number of Participants:

A total of 56 study participants will be included into the two parts of the study as follows:

1.1.6.1. Part 1 Participant Numbers

In Part 1, approximately 6 participants will be given Palivizumab for an estimated total of 6 evaluable participants. To ensure the number of evaluable participants is reached in each part of the study, refer to the Participant Replacement Policy (Section 7.4),

1.1.6.2. Part 2 Participant Numbers

In this RSV prophylactic treatment Part 2, it is anticipated that no participants will drop out between study intervention treatment on Day -1 and RSV inoculation on Day 0. Approximately 50 participants will be randomly assigned to study intervention for an estimated total of 50 evaluable participants. To ensure the number of evaluable participants is reached in each part of the study, refer to the Participant Replacement Policy (Section 7.4).

Note: A participant will be considered to be `enrolled` into the study once he/she has been randomised.". Potential participants who are screened for the purpose of determining suitability for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

1.1.7. Intervention Groups and Duration:

The study will be performed in two parts:

1.1.7.1. Part 1 Interventions & Duration

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).

1.1.7.2. Part 2 Interventions & Duration

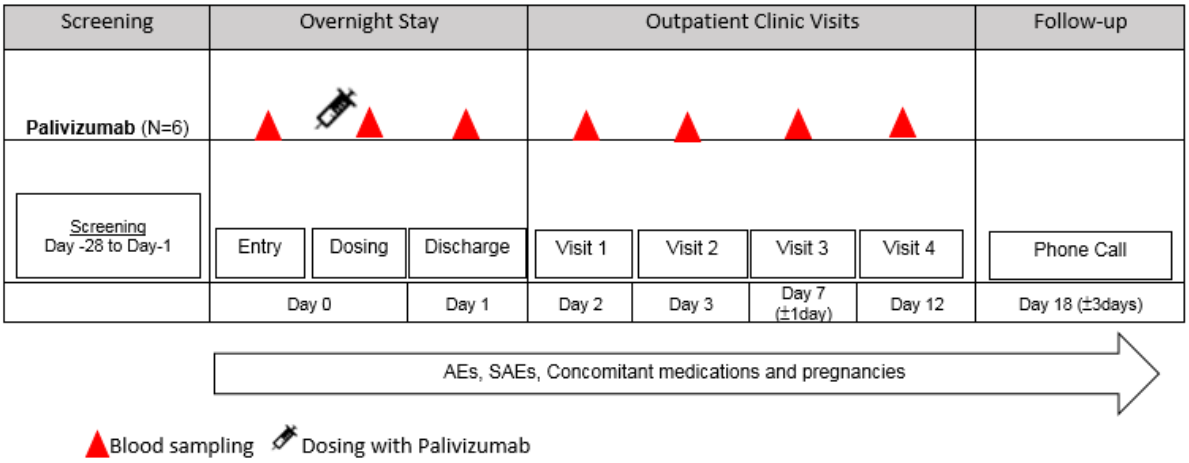
The total duration of study participation for a participant is up to approximately 122 days, with the following sequence and duration of study periods:

- **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)

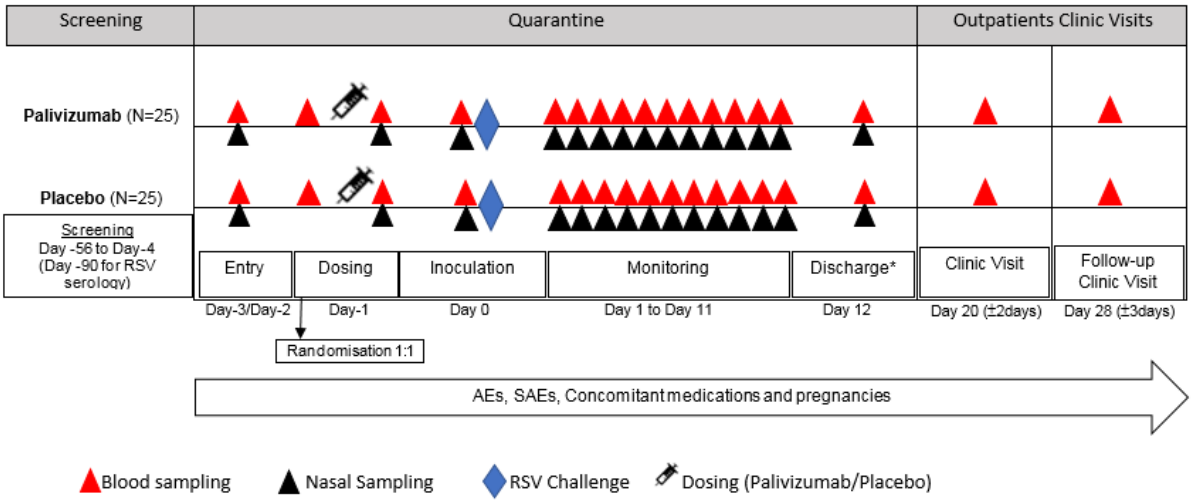
- **Inpatient phase:** Participants will be resident in the Quarantine Unit for approximately 16 days (from Day -3 to Day 12). Procedures will include:
    - **Pre-human viral challenge (HVC)**:
        - Admission to Quarantine Unit on Day -3
        - Study intervention I.V. dosing on Day -1
    - **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)

1.2. Study Schematic: On-study Participant Progression

Part 1



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.

1.3. Schedules of Activities (SoA)

1.3.1. Part 1 SoA

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)	◄———	———	———	———	———	———	———	———►

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.

1.3.2. Part 2 SoA

Study Phase	Screening Phase*	QUARANTINE ISOLATION																		Clinic visit		Early withdrawal visit
		Admission to quarantine		Dosing	Human Viral Challenge (HVC)			Post HVC Days											Discharge			
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	Challenge	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

hVIVO template identifier: (G_0687) v3.0

Study Phase	Screening Phase*	QUARANTINE ISOLATION																			Clinic visit		Early withdrawal visit
		Admission to quarantine		Dosing	Human Viral Challenge (HVC)			Post HVC Days												Discharge			
Tympanic temperature	X	X	TDS	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	TDS	X			
24-hour tissue count & nasal discharge weight (c)				X	X			X	X	X	X	X	X	X	X	X	X	X	X	X			(X)
12-lead ECG	X	X[I]		X[0]							X			X				X				X	X
Spirometry (d)	X	X[I]		X	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	X
FOT (d)			(X)	(X)	(X)			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)			
Patient Health Questionnaire (PHQ-9)	(X)	(X)[I]																					
Generalised Anxiety Disorder Questionnaire (GAD-7)	(X)	(X)[I]																					
Product Administration																							
Randomisation				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[I]																					(X)
HIV, Hepatitis A, B, & C	X																						

hVIVO template identifier: (G_0687) v3.0

Study Phase	Screening Phase*	QUARANTINE ISOLATION																Dis charge	Clinic visit		Early withdrawal visit
		Admission to quarantine		Dosing	Human Viral Challenge (HVC)			Post HVC Days													
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				
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).

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+	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.
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. Allowable time windows are described I section 8.19.3.
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. Allowable time windows are described I section 8.19.4.
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.

GENOMIC, TRANSCRIPTOMIC AND PROTEOMIC SAMPLES				
DNA/RNA/proteomic sample collection:	Yes	☐	No	☒
	n/a			
Consent considerations:	Future use of remaining samples for new ethically approved health research and laboratory testing protocols according to the local laws.			

2. Introduction

2.1. Background

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

It should be noted that RSV is also increasingly being recognised as a significant cause of morbidity and mortality in older adults and those with underlying chronic cardiopulmonary disorders (Falsey et al. 1995; Agius et al. 1990; Falsey et al. 2005).

The RSV human challenge model was developed to not only aid understanding of RSV disease, but to also assess the efficacy of RSV antivirals, immunomodulators and vaccines. The RSV-A Memphis 37b challenge strain has been used for over 10 years by both hVIVO and others and has helped assess the efficacy of numerous RSV therapies and vaccines (Lambkin-Williams et al. 2018). Specifically, hVIVO have safely and successfully used the RSV challenge strain in over 1220 healthy participants (18 to 55 years of age) and have also safely completed inoculation of twenty-four participants between 60 and 75 years of age. Additionally, another strain of live RSV (Memphis 37c) has been used as an inoculation agent and was shown to be safe in over 77 healthy young adults across three studies. RSV infection was not associated with any serious adverse side effects. Healthy RSV challenge study participants have approximately 65% to 85% chance of becoming infected with RSV following the administration of the virus (DeVincenzo et al. 2010). Typical RSV illness is characterised by an abrupt onset of rhinitis, nasal stuffiness, fever, malaise, myalgia (muscle aches), and sore throat. In healthy adults, the illness usually resolves without any treatment, with relief of symptoms occurring naturally within 7 to 10 days.

Palivizumab (Synagis™), a humanised monoclonal antibody directed against RSV, has been shown to be effective in reducing hospitalisation due to RSV by approximately 50% in high-risk infants who receive monthly immunoprophylaxis. While several clinical studies with Palivizumab were performed in adults, it is not currently licensed for use in adults. A full summary of the preclinical and clinical experience with Palivizumab (Synagis™). can be found in the Summary of Product Characteristics (SmPC) and “PALIVIZUMAB Summary of relevant clinical and non-clinical data to support the use of Investigational Medicinal Product (IMP) in the clinical trial” document supplementing the SmPC.

2.2. Study Rationale

There are currently no effective vaccines to prevent RSV in children, and treatment options for RSV-infected individuals are limited. Palivizumab is currently licensed for immunoprophylaxis against RSV in young high-risk children, requiring 5 monthly doses and is not affordable in LMICs. The high costs of Palivizumab (US$9600/per season in the USA, and €5000 in Europe) make this biotherapeutic product unaffordable for children in LMICs, which are the areas where the virus is most prevalent and the associated mortality rates are the highest. According to data from The Lancet (Nair et al. 2010), between 66,000 and 199,999 children died from complications stemming from RSV in 2005. 99% of those deaths were recorded in developing countries. Therefore, in order to provide effective and affordable RSV immunoprophylaxis for young high-risk children in LMICs, biosimilars for Palivizumab are being developed. Biosimilars are medicines of an equivalent nature in terms of quality, effectiveness and safety to their benchmark biologics that are developed once the patent on the original product has expired, thereby enabling the price to be lowered significantly.

In 2014, the WHO and the Utrecht University in The Netherlands agreed on a technical collaboration [Memo of Understanding (MOU)] which will contribute to the goal in promoting the wide availability of safe, effective, and affordable biotherapeutics in particular in the public sector of developing countries. Based on this memorandum, Utrecht University established the Utrecht Centre for Affordable Biotherapeutics for Public Health (UCAB), as a central hub to facilitate the development of safe and affordable biotherapeutics for low- and middle-income countries in a sustainable way. UCAB collaborates with mAbxience and local manufacturers in low- and middle-income countries in the development of the palivizumab biosimilar. As such, mAbxience together with the Utrecht Centre for Affordable Biotherapeutics for Public Health (UCAB) have received the mandate from WHO to develop this biosimilar palivizumab, MB05.

No data exists for Palivizumab in the RSV human challenge model. Further to scientific advice received from the European Medicines Agency (EMA), this exploratory study is intended to establish the margins of effect and variance of prophylactically administered Palivizumab within the RSV-A Memphis 37b challenge model in healthy adult volunteers. This will enable subsequent evaluation of biosimilars (such as MB05) for prophylactic equivalence or non-inferiority to the reference article (Palivizumab), in the RSV human challenge model.

Furthermore, this study will explore the minimal clinically important differences (MCID) between the reference article Palivizumab and Placebo treated groups after inoculation with RSV. The MCID is defined as the smallest difference in score in the outcome of interest that informed what patients or proxies perceive as important, and which would lead the patient or clinician to consider a change in the management (Schunemann and Guyatt 2005). The data obtained from this study will aid in developing MCIDs for each endpoint measure, as appropriate.

The rationale for the study design is presented in Section 4.2.

Please refer to the SmPC for a full summary of the preclinical and clinical experience with Palivizumab (Synagis™).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Palivizumab may be found in SmPC; although possible. Side effects of Palivizumab have been established in paediatric population at high risk of severe RSV infection following an intramuscular

(IM) administration of Palivizumab. Historical studies in 48 healthy adults (CDER_FDA 2004) using liquid and lyophilised Palivizumab administered as both Intramuscular (IM) and IV injections have reported no serious adverse events (SAEs). The most common side effect observed in adults was mild transient dizziness and headache.

2.3.1. Risk Assessment

The known risks to participants are detailed in Table 1. However, there may also be risks that are unforeseen and not anticipated (e.g., unknown allergies). Every effort will be made to monitor the health of the participants to ensure that such risks are minimised. Trained medical personnel and facilities will be available to provide medical emergency care.

Table 1 - Risk Assessment

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
Study Intervention		
Intravenous Dosing with Palivizumab	Local signs and symptoms associated with the injection may include: erythema, swelling/induration, and pain/tenderness at the injection site.	Local reactions will be monitored but are generally short-term and do not require treatment.
	Other side effects include rash	Side effects will be monitored but are generally short-term and do not require treatment.
	Other less common but serious side effects reported include anaphylaxis and anaphylactic shock and other severe acute hypersensitivity reactions	Medications (e.g epinephrine) will be available in the clinic to treat serious allergic reactions promptly. Participants with a known allergy, or history of anaphylaxis or other serious adverse reactions will be excluded from the study. The study site should have medical treatment available in case of severe allergic reactions.
	Systemic exposure to Palivizumab	To minimise any risks associated with systemic exposure to Palivizumab, male and female participants must be on highly effective contraception methods during the study and up to 90 days post dosing with Palivizumab.
	Lack of pre-clinical reproductive toxicity evaluation as well as clinical toxicity evaluations in pregnancy due to target population indication (high-risk children <24 months) of Palivizumab and requirements for licensing for indication. Although reproductive toxicity studies are	Participants will be advised to use appropriate methods of contraception during the study and for 90 days after administration of Palivizumab for male participants (equivalent to the sperm life cycle) and 30 days for female

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
	not considered appropriate for the study intervention.	participants (equivalent to the length of a menstrual cycle).
	Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. In addition, Palivizumab inhibits virus replication in cell culture, and therefore may also interfere with viral culture assays. Palivizumab does not interfere with reverse transcriptase-polymerase chain reaction-based assays. Assay interference could lead to false-negative RSV diagnostic test results. Therefore, diagnostic test results, when obtained, should be used in conjunction with clinical findings to guide medical decisions	Discharge from quarantine will utilise a PCR based test instead of an antigen test. PCR based tests will be used to confirm the incidence of infection and to quantify virus shed by infected participants. Implications for culture-based quantification of RSV will be assessed.
Study procedures		
Blood Sampling	Pain or bruising at the site where blood is drawn.	Blood samples will be obtained by a trained professional.
	Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle insertion.	Blood samples will be obtained by a trained professional and procedures will be put in place to avoid injury from fainting.
	There is a possibility that in the process of collecting blood a nerve may be injured.	Procedure to be performed by qualified personnel.
	Blood tests performed to address the health of the participants at screening and during the study may indicate that a participant has an infection that he/she was not previously aware of (such as HIV or hepatitis) or an unexpected illness.	The hVIVO doctor will provide the participant's general practitioner (GP), or doctor with a referral letter if the participant agrees.
Nasal sampling	Collection of nasal wash samples or nasopharyngeal swabs may cause discomfort, sneezing, watery eyes, irritated nose or nose bleeding.	Sample collection will be performed by appropriately qualified and trained study staff to minimise the discomfort.

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
RSV infection from inoculation		
RSV infection & severe complications	65% to 85% chance of becoming infected with RSV. Typical RSV illness: abrupt onset of rhinitis, nasal stuffiness, fever, malaise, myalgia (muscle aches), and sore throat. Severe RSV infections are known to occur in both infants and adults. In adult populations, multiple factors but not older age, are independently associated with severe RSV complications including persons of any age with chronic co-morbidities and significant immune compromise. The study virus, like many viruses, can cause more substantial health issues such as myocarditis (inflammation or damage to the heart muscle). However, the chance of this resulting in serious or permanent changes is rare, as most cases are minor and resolve without any lasting changes. In previous virus challenge studies at hVIVO, uncommonly (3 cases in more than 1000 individuals who have received the challenge virus) blood tests have shown a change suggestive of myocarditis, although in these few participants the blood tests returned to normal without treatment.	The safety profile of the RSV-A Memphis 37b challenge strain is well characterised in healthy young adults as this has been used for over ten years by hVIVO. At hVIVO more than 1000 healthy adults aged 18 to 55 years have been challenged with the RSV-A Memphis 37b strain. RSV infection in healthy adults usually resolves without treatment within 7 to 10 days. Strict inclusion and exclusion criteria will apply to ensure only healthy adults are enrolled in this study. There will be a daily medical monitoring in a quarantine unit for at least 12 days post-challenge. Qualified medical and nursing staff in the quarantine unit will monitor for, and manage any symptoms Participants will be closely followed up while being in quarantine. Electrocardiogram will be performed, and cardiac enzymes will be tested at least 4 days, 7 days and 11 days post-viral challenge
	Transient increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) without clinical presentation, with a good prognosis upon improvement of infection.	ALT and AST will be monitored.
Transmission of RSV to participants' close contacts	RSV virus in nasal secretions can cause infection in close contacts.	Virus is usually absent from the nose by the time participants are discharged from quarantine. This will be confirmed by testing a nasal sample using PCR to determine participants' suitability for departure.
	Passing the RSV Challenge Virus to others, including vulnerable people (see below for definition of vulnerable populations).	To reduce the risk, participants will be asked to avoid, where possible, contact with vulnerable people for 14 days after they leave quarantine (Section 2.3.1.1).

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
	Passing the RSV Challenge Virus to study staff.	Clinic staff in contact with participants in the quarantine unit will require to wear Personal Protective Equipment (PPE) to avoid the transmission of the RSV Challenge Virus to study staff and to prevent the risk of cross-contamination by a viral disease being brought up into the unit by staff.
Risk of reactivation of herpes infection.	If a participant ever had a herpes infection (e.g., cold sores, genital herpes or shingles), there is a small possibility that this infection could return after challenge.	Participants will be instructed to inform the study staff if they currently have an active herpes infection or have had one during the 30 days before enrolment.
Please consult the SmPC for Palivizumab (Synagis) for detailed information.		

2.3.1.1. Vulnerable persons

For the purposes of possible contact, a vulnerable individual is a person who has close or household (i.e., share the same apartment or house) high-risk contacts including but not limited to:

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

2.3.2. Benefit Assessment

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

Participants may develop some temporary immunity to RSV through treatment with Palivizumab and benefit from a general health check at Screening. Benefit may also be derived from the medical evaluations and assessments associated with study procedures. In addition, participants are contributing to the process of developing new therapies in an area of unmet medical need.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants in this study, the potential risks are justified by the anticipated benefits linked to the evaluation of the margin and variability of Palivizumab in a viral challenge model which will subsequently facilitate future assessment of biosimilars for prophylactic bioequivalence or non-inferiority to Palivizumab.

3. Objectives and Endpoints

3.1. Part 1 Objectives and Endpoints

Objectives	Endpoints
• To confirm the dose of Palivizumab to be given to participants in Part 2	• Evaluation of PK levels after intravenous administration of Palivizumab
• To assess safety of Palivizumab in healthy adults	• 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)

3.2. Part 2 Objectives and Endpoints

Objectives	Endpoints
• 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 quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR)].	The margin and variance will be estimated as follows: • 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.
• 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)].	The margin and variance will be estimated as follows: • 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.
• 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)].	The margin and variance will be estimated as follows: • 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.

Objectives	Endpoints
• 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)].	The margin and variance will be estimated as follows: ○ 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.
• 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].	The margin and variance will be estimated as follows: • 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.
• 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].	The margin and variance will be estimated as follows: ○ Occurrence of 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. ○ Occurrence of 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. ○ 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. ○ 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. Similar endpoints may be evaluated based on quantitative viral culture assay.
• 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	The margin and variance will be estimated as follows: • Incidence of symptomatic RSV infection, as defined by:

Objectives	Endpoints
Placebo [assessed by symptomatic infection in terms of incidence, duration, and peak].	○ Incidence of infection, and ○ At least one grade 2 symptom from one or more respiratory categories from the participant symptom diary card. • Number of days with symptoms of grade 2 or more, starting one day post-viral challenge (Day +1) up to the end of quarantine. • 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.
• To assess safety of Palivizumab in the RSV human challenge model in healthy adults	• 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)
• To assess the pharmacokinetics of Palivizumab in the RSV human challenge model in healthy adults	• Palivizumab serum concentrations and serum PK parameters through study Day +28 • Nasal concentrations and serum PK parameters through study Day +28
• To assess the Anti-Palivizumab antibody (ADA) in the RSV human challenge model in healthy adults	• Anti-Palivizumab antibody (ADA) through Day 28
Tertiary/Exploratory	
• To explore lung function changes in relation to RSV infection	• Assessments of spirometry, PEF, and FOT
• 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"
• 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

Objectives	Endpoints
	• Response to Palivizumab treatment
• To explore the host-pathogen relationship in the RSV human challenge model in healthy adults	• Immune assays related to Palivizumab • RSV baseline immunity and immune responses to infection

4. Study Design

4.1. Overall Design

This is an exploratory study in healthy adult participants aged 18-55 years. The study is formed of two parts, Part 1 and Part 2.

4.1.1. Part 1 design

All participants in Part 1 will receive the following on Day 0:

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

If there are no safety concerns in Part 1, and PK analysis of Palivizumab treated participants confirm 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 insufficient dose to provide suitable efficacious coverage in Part 2, then Part 2 will proceed with a dose of 15mg/Kg.

4.1.2. Part 2 design

Participants in Part 2 will be pre-screened for susceptibility to RSV infection, i.e., have levels of RSV neutralising antibodies compatible with susceptibility to RSV infection (the cut-off is based on the average 25th percentile of the past 12 months screening results).

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 $\log_{10}$ plaque forming unit, given intranasally

The Study Schematic - showing participant progression through the study - is presented in Section 1.2; the Schedules of Activities (SoA) are presented in Section 1.3.

4.1.3. Part 1 duration

The total duration of study participation for a participant is up to approximately 52 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 I.V. dosing on Day 0
    - Post infusion monitoring and PK Day 0 and Day1
    - 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 Day 12
    - Final safety follow-up by telephone: Day 18 (±3 days).

4.1.4. Part 2 duration

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-HVC**:
        - Admission to Quarantine Unit on Day -3
        - Study intervention I.V. dosing on Day -1
    - **HVC**:
        - Challenge Virus inoculation on Day 0 (window 1 to 2 days post-treatment)
    - **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 Day12 (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)

The study will be conducted by hVIVO which has extensive experience with RSV challenge studies. Numerous studies have been performed using experimental RSV infection in human participants. To date, in hVIVO's studies, over 1220 healthy participants (18 to 55 years of age) have been successfully and safely inoculated with RSV-A Memphis 37b. These studies demonstrated that adults could be infected by nasal inoculation and that experimental infection was safe. This strain has been shown to cause symptoms and virus shedding that closely match natural infection.

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

4.2. Scientific Rationale for Study Design

This RSV Memphis 37b strain has been shown to cause symptoms and virus shedding that closely match natural infection in otherwise healthy adults.

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

4.3. Justification for Treatment Dose & Route of Administration

The dose regimen of 8mg/kg in part 1 and 8mg/kg or 15mg/kg Palivizumab in part 2 of the study is supported by data from previous clinical trials and human experience referenced in this protocol, SmPC and the accompanied document "PALIVIZUMAB Summary of relevant clinical and non-clinical data to support the use of IMP in the clinical trial".

Studies performed in adult volunteers showed that the half-life of elimination of the drug was approximately 17-20 days when administered either IV or IM and was safe through at least three-monthly injections (with the upper most test dose of 15 mg/kg). There were no safety signals in the adult volunteer studies. A single IV dose in adult volunteers at twice the recommended palivizumab prophylaxis dose has been shown to be well tolerated.

Details of clinical studies to examine the comparability of the human safety, tolerability, immunogenicity and pharmacokinetics characteristics of the liquid and the lyophilized preparations of Synagis are listed in accompanied document "PALIVIZUMAB Summary of relevant clinical and non-clinical data to support the use of IMP in the clinical trial".

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA relevant for each part of the study or the last unscheduled visit as applicable. If a safety visit is required after the last scheduled visit, this will be at the PI's discretion as a duty of care, e.g., repeat spirometry or laboratory tests. These discretionary follow-up visits will not be considered part of the trial data unless they represent follow-up and closure on an AE or serious adverse event (SAE) identified during the trial period.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

NO	INCLUSION CRITERIA
1	An informed consent document signed and dated by the participant and the Investigator.
2	Aged between 18 and 55 years old on the day of signing the consent form.
3	In good health with no history, or current evidence, of clinically significant medical conditions, and no clinically significant test abnormalities that will interfere with participant safety, as defined by medical history, physical examination, (including vital signs), Electrocardiogram (ECG), and routine laboratory tests as determined by the Investigator.
4	A documented medical history prior to enrolment.
5	The following criteria are applicable to female participants participating in the study. a) Females of childbearing potential must have a negative pregnancy test prior to enrolment. b) Females of non-childbearing potential: a. Post-menopausal females; defined as having a history of amenorrhea for >12 months with no alternative medical cause, and /or by FSH level >40mIU/mL, confirmed by laboratory. b. Documented status as being surgically sterile (e.g. tubal ligation, hysterectomy, bilateral salpingectomy and bilateral oophorectomy).
6	The following criteria apply to female and male participants: a) Female participants of **childbearing potential** must use **one form** of highly effective contraception. Hormonal methods must be in place from at least 2 weeks prior to the first study visit. The contraception use must continue until 30 days after the date of viral challenge/last dosing with IMP (whichever occurs last). Highly effective contraception is as described below: a. Established use of hormonal methods of contraception described below (for a minimum of 2 weeks prior to the first study visit). When hormonal methods of contraception are used, male partners are required to use a condom with a spermicide:

	i. combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: 1. oral 2. intravaginal 3. transdermal ii. progestogen-only hormonal contraception associated with inhibition of ovulation: 1. oral 2. injectable 3. implantable b. Intrauterine device (IUD) c. Intrauterine hormone-releasing system (IUS) d. Bilateral tubal ligation e. Male sterilisation (with the appropriate post vasectomy documentation of the absence of sperm in the ejaculate) where the vasectomised male is the sole partner for that woman. f. True abstinence - sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. b) Male participants must agree to the contraceptive requirements below at entry to quarantine and continuing until 90 days after the date of Viral challenge / last dosing with the investigational medicinal product (IMP) (whichever occurs last): a. Use a condom with a spermicide to prevent pregnancy in a female partner or to prevent exposure of any partner (male and female) to the IMP. b. Male sterilisation with the appropriate post vasectomy documentation of the absence of sperm in the ejaculate (*please note that the use of condom with spermicide will still be required to prevent partner exposure).* This applies only to males participating in the study. c. In addition, for female partners of child bearing potential, that partner must use another form of contraception such as one of the highly effective methods mentioned above for female participants. d. True abstinence - sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. c) In addition to the contraceptive requirements above, male participants must agree not to donate sperm following discharge from quarantine until 90 days after the date of Viral Challenge/last dosing with IMP (whichever occurs last).

7	**For Part 2 of the study:** Sero-suitable to the challenge virus, as defined in the study Analytical Plan.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

NO	STANDARD EXCLUSION CRITERIA
Medical History	
1	History of, or currently active, symptoms or signs suggestive of upper or lower respiratory tract infection within 4 weeks prior to the first study visit.
2	a) Any history or evidence of any other clinically significant or currently active systemic comorbidities including psychiatric disorders (includes participants with a history of depression and/or anxiety). b) And/or other major disease that, in the opinion of the Investigator, may put the participant at undue risk, or interfere with a participant completing the study and necessary investigations. *The following conditions apply:* • *Participants with clinically mild atopic eczema/atopic dermatitis and clinically mild psoriasis may be included at the Investigator's discretion (e.g., if small amounts of regular topical steroids are used, no eczema in cubital fossa; moderate to large amounts of daily dermal corticosteroids is an exclusion).* • *Rhinitis (including hay fever) which is clinically active or history of moderate to severe rhinitis, or history of seasonal allergic rhinitis likely to be active at the time of inclusion into the study and/or requiring regular nasal corticosteroids on an at least weekly basis, within 30 days of admission to quarantine will be excluded. Participants with a history of currently inactive rhinitis (within the last 30 days) or mild rhinitis may be included at the PI's discretion.* • *Participants with a physician diagnosed underactive thyroid who have been controlled on treatment for at least 6 months with evidence of a normal thyroid function test (TFT) can be included at the discretion of the PI.* • *Any concurrent serious illness including history of malignancy that may interfere with the aims of the study or a participant completing the study. Basal cell carcinoma within 5 years of initial diagnosis or with evidence of recurrence is also an exclusion.* • *Participants with a history of psychiatric illness including depression and/or anxiety of any severity within the last 2 years can be included if the Patient Health Questionnaire (PHQ-9) and / or the Generalised Anxiety Disorder Questionnaire (GAD-7) is less than or equal to 4. Participants with a PHQ-9 or GAD-7 score of*

NO	STANDARD EXCLUSION CRITERIA
	between 5 and 9 may be included following consultation with a Senior Physician (Clinical Lead for Screening) who may advise further consultation with the PI. • *Participants reporting physician diagnosed migraine can be included provided there are no associated neurological symptoms such as hemiplegia or visual loss. Cluster headache/migraine or prophylactic treatment for migraine is an exclusion.* • *Participants with physician diagnosed mild Irritable Bowel Syndrome (IBS) not requiring regular treatment can be included at the discretion of the PI.*
3	Participants who have smoked ≥ 10 pack years at any time [10 pack years is equivalent to one pack of 20 cigarettes a day for 10 years]).
4	A total body weight ≤ 50 kg and Body Mass Index (BMI) ≤18 kg/m2 and ≥30kg/m^2.
5	Females who: a) Are breastfeeding, or b) Have been pregnant within 6 months prior to the study.
6	History of anaphylaxis-and/or a history of severe allergic reaction or significant intolerance to any food or drug, as assessed by the PI.
7	Venous access deemed inadequate for the phlebotomy and cannulation demands of the study.
8	a) **For Part 2 of the study:**Any significant abnormality altering the anatomy of the nose in a substantial way or nasopharynx that may interfere with the aims of the study and in particular any of the nasal assessments or viral challenge, (historical nasal polyps can be included, but large nasal polyps causing current and significant symptoms and/or requiring regular treatments in the last month will be excluded). b) Any clinically significant history of epistaxis (large nosebleeds) within the last 3 months of the first study visit and/or history of being hospitalized due to epistaxis on any previous occasion. c) Any nasal or sinus surgery within 3 months of the first study visit.
Prior or Concomitant Medications and Assessments	
9	**For Part 2 of the study:** a) Evidence of vaccinations within the 4 weeks prior to the planned date of viral challenge/first dosing with IMP (whichever occurs first). b) Intention to receive any vaccination(s) before the last day of Follow-up. (NB. No travel restrictions will apply after the Day 28 (±3 days) Follow-up Visit).
10	Receipt of blood or blood products, or loss (including blood donations) of 470 mL or more of blood during the 3 months prior to the planned date of viral challenge/first dosing with IMP (whichever occurs first) or planned during the 3 months after the final visit.
11	a) Receipt of any investigational drug within 3 months prior to the planned date of viral challenge/first dosing with IMP (whichever occurs first).

NO	STANDARD EXCLUSION CRITERIA
	b) Receipt of three or more investigational drugs within the previous 12 months prior to the planned date of viral challenge/first dosing with IMP (whichever occurs first). **For Part 2 of the study:** c) Prior inoculation with a virus from the same virus-family as the challenge virus. d) Prior participation in another human viral challenge study with a respiratory virus in the preceding 3 months, taken from the date of viral challenge in the previous study to the date of expected viral challenge in this study.
12	a) Confirmed positive test for drugs of abuse on first study visit. One repeat test allowed at PI discretion. b) History or presence of alcohol addiction, or excessive use of alcohol (weekly intake in excess of 28 units alcohol; 1 unit being a half glass of beer, a small glass of wine or a measure of spirits), or excessive consumption of xanthine containing substances (e.g. daily intake in excess of 5 cups of caffeinated drinks e.g. coffee, tea, cola).
13	**For Part 2 of the study:** A forced expiratory volume in 1 second (FEV1) < 80%.
14	Positive human immunodeficiency virus (HIV), active hepatitis A (HAV), B (HBV), or C (HCV) test.
Other	
15	Those employed or immediate relatives of those employed at hVIVO or the Sponsor.
16	Any other finding that, in the opinion of the Investigator, deems the participant unsuitable for the study.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

No dietary restrictions are required before or after dose administration.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants must abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours prior and during quarantine and for 48 hours prior to all visits requiring spirometry.

Participants must not consume alcohol for 72 hours prior and during quarantine and for 72 hours prior to any clinic visits.

Participants must not smoke, use tobacco or any nicotine containing products for 72 hours prior to and during quarantine Participants that are current smokers may be continued in the study if, in the opinion of the PI, cessation of smoking during quarantine will not lead to withdrawal symptoms which could interfere with the accurate recording on the Symptoms Diary Card.

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours prior and during quarantine and for 48 hours prior to each clinic visit (unless it is within the usual activity of the participant).

5.4. Screen Failure

Screen failures are defined as participants who sign the study specific Informed Consent Form (ICF) but are not subsequently randomised to receive the study Intervention.

For individuals who do not meet the criteria for participation in this study (screen failure), the Investigator will decide whether the participant should be permanently excluded from the study or invited back for repeat assessments (i.e. repeat clinical laboratory test) if the initial screening assessments are still within the allowed screening windows (-28 to -1 days for Part 1 and -56 to -4 days for Part 2) or rescreening for a later quarantine, as appropriate.

6. Study Intervention

Study interventions administered to participants are described in Table 2.

6.1. Study Intervention(s) Administered

Table 2 - Study Interventions

Intervention Name	Palivizumab	Placebo	RSV-A Memphis 37b virus
Type	Biologic	Other	Virus
Dose Formulation	Liquid solution (50mg or 100mg) in sterile water for injection to give a final concentration of 20mg/mL	Sodium Chloride 0.9% Solution (Normal Saline)	Cryovial, Liquid
Unit Dose Strength(s)	• 8 mg/kg for Part 1 • 8mg/kg or 15 mg/kg for Part 2	Not applicable	The inoculum virus titre is determined in an infectivity (plaque) assay, the titre is reported in plaque forming units per mL (PFU/mL). The challenge dose is approximately 4.5log_{10} PFU.
Dosage Level(s)	• A single dose of 8mg/Kg, or • A single dose of 15mg/Kg	• A single dose of 0mg/Kg	A single dose of virus will be delivered. Dose volume delivery method is provided in the Analytical Plan
Route of Administration	Infusion IV	Infusion IV	Intranasal
Use	Reference article	Placebo control	Infectious Challenge agent
IMP and NIMP	IMP	IMP (Placebo)	NIMP Challenge virus
Sourcing	Sponsor	Provided centrally by hVIVO	Provided centrally by hVIVO
Packaging and Labelling	Study intervention will be provided as	Study intervention will be provided as	RSV Challenge Inoculum will be provided in vials. The

	individual doses in single use sterile Latex/DEHP Free syringes, prepared, labelled and QP released by Hammersmith Medicines Research (HMR) Pharmacy (London) holding MIA (IMP) licence.	individual doses in single use sterile Latex/DEHP Free syringes, prepared, labelled and QP released by Hammersmith Medicines Research (HMR) Pharmacy (London) holding MIA (IMP) licence.	details of the virus challenge agent packaging and labelling will be provided in the Analytical Plan
Current/Former Name(s) or Alias(es)	Synagis ™	n/a	n/a

All supplies indicated in Table 2 will be provided per the "Sourcing" row depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (e.g. not applicable in the case where multiple lots or batches may be required due to the length of the study).

Refer to Section 6.2 and the pharmacy manual for details regarding administration of the study intervention.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Dose Preparation

Storage and manufacture of the Investigational product will be based on SmPC. Palivizumab and placebo will be prepared by an unblinded pharmacist for each individual participant. Dose preparation procedures will be described in the pharmacy manual and as described in Hicks *et al*. (Hicks, Chemaly, and Kontoyiannis 2003).

6.2.2. Handling, Storage, and Accountability

Interventional Product / Placebo:

Bulk supplied of the Investigational product will be stored at HMR Pharmacy. Individual ready-to-dispense Interventional product / Placebo doses will be prepared by unblinded pharmacist, Qualified Person (QP) released and delivered to hVIVO prior to administration of the treatment to the participant.

HMR Pharmacy and hVIVO will maintain drug accountability as detailed in the Pharmacy Manual.

The Investigator will ensure that all supplies are received by a responsible person, all deliveries and returns are documented and signed for, and the condition of the Interventional product / Placebo is monitored. Accurate records will be kept of when and how much Interventional product / Placebo is dispensed and used in the study. Any reasons for departure from the protocol dispensing regimen must be recorded.

Accountability records will be available for verification by the Study Monitor at each monitoring visit. At the completion of the study, there will be a final reconciliation of all Interventional product / Placebo.

Challenge Virus

The RSV-A Memphis 37b challenge virus was produced via a nasal aspirate collected from a paediatric patient infected with RSV. The Challenge Virus stock, RSV-A Memphis 37b, was manufactured under current good manufacturing practices (cGMP). The Challenge Virus stock has undergone quality testing performed during manufacturing (identity, appearance, sterility, infectivity, and contaminants) according to pre-determined specifications, and has subsequently also passed an extensive panel of adventitious agent testing. The Challenge virus is stored in a secure -80°C freezer (normal temperature range -60°C to -90°C).

Challenge Virus inoculum will be prepared according to the hVIVO Analytical Plan (AP) and administered in accordance with hVIVO's standard operating procedures (SOPs). Each participant will be allocated a unique vial containing the Challenge Virus and will receive the inoculum intranasally.

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

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

All study interventions:

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention
2. Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records)
4. Disposal of used and unused Challenge Virus inoculum vials will be in accordance with hVIVO's SOPs
5. Unless specifically instructed by Sponsor, the Investigator will not destroy any partly used or unused IMP supply. On written authorisation from the Sponsor, the Investigator will send unused and partly used IMP supplies and any empty containers for destruction to the address provided at the time of authorisation. Alternatively, the destruction of unused and partly used drug supplies and any empty containers may be facilitated by the Investigator using a partner service, according to local procedures, and a destruction certificate will be provided.

6.3. Randomisation and Blinding

hVIVO assigns a unique 6 digits number to each participant in the hVIVO database. This number will be used to identify a participant up to the point of randomisation, on source documents, on all study correspondence and in the study database. In Part 2 of the study, a separate randomisation number will be allocated to the participants at randomisation and will be used for allocation of study intervention (Palivizumab or Placebo).

In Part 2, a computer-generated randomisation schedule will be generated using SAS. Once assigned, that randomisation number shall not be reassigned.

Randomisation numbers will follow a 3-digit format e.g., [001]. A copy of the randomisation code list will be sent to the unblinded pharmacist preparing the study intervention, so that study intervention/placebo can be prepared for each participant as appropriate. The randomisation number encodes the participant's assignment to receive Palivizumab or Placebo in a 1:1 ratio.

Each participant will be dispensed blinded study intervention, labelled with his/her unique randomisation number, throughout the study. With the exception of the unblinded pharmacist, the unblinded statistician preparing the randomisation code list, the unblinded Clinical Research Associate (CRA) and the Quality Assurance (QA) auditors where necessary, the Investigator and all other clinical and non-clinical staff, (including the Study Statistician, data management staff), and the participants will remain blinded to the treatment allocation until after the database has been locked and approval for study unblinding has been given.

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

Participants who are replaced as per Section 7.4 Participant Replacement Strategy will be replaced and assigned a new, unique randomisation number equaling the randomisation number of the replaced participant, plus 100. This will ensure that the replacement participant receives the same allocated, blinded treatment as the participant who is being replaced.

An individual access to a secured website will be provided to the Investigator. The website, compliant with 21CFR part 11 guidelines, will be used in the event that unblinding is required. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. When the investigator breaks the code, they will have to indicate on the website the reason for unblinding. The person who carried out the unblinding and the date and time of code breaking will be automatically recorded. After confirmation of the code break, the treatment allocation will appear on the screen. A notification with the treatment allocation will also be provided by email. A notification, without the treatment allocation, will be provided to the study team. Furthermore, the Sponsor must be notified within 24 hours after breaking the blind. Once the study is complete, the unblinded database will be provided to the Sponsor.

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

The study intervention must be discontinued after unblinding, but the participant will be followed up until resolution of any AEs.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention and challenge virus directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the case report form (CRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

Any non-compliance or problems with the administration of the study intervention will be recorded in the participant's source notes and reported to the Sponsor if appropriate.

6.5. Concomitant Therapy

Any medications taken and changes in medications from the time the participant signing the study specific informed consent, up to final study contact Day 28 (±3 days) will be recorded in the source data. Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest) that the participant is receiving at the time of enrolment or receives during the quarantine/outpatient stage will be stored, prescribed and administered in line with their label-specific requirements, and recorded according to the parameters required by the clinical database.:

Participants will be reminded to refrain from using any over-the-counter medication without the approval of the Investigator and must notify the site as soon as possible if they are prescribed any medication. All medications must be stopped prior to the planned date of dosing with IMP/viral challenge (whichever occurs first) unless in the opinion of the Investigator and/or Sponsor's Medical Expert (SME), the medication will not interfere with the study procedures or compromise participant safety.

Medications prohibited throughout the study are shown in Table 3.

Table 3 - Prohibited Medications

Prohibited medication	Washout
Systemic (oral and parenteral) antiviral drugs.	4 weeks prior to first study visit.
Use or anticipated use during conduct of the study of concomitant medications (prescription and non-prescription), including vitamins or herbal and dietary supplements within the specified windows, unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise participant safety.	7 days prior to the planned date of viral challenge: •Herbal supplements •Any medication or product (prescription or over the counter) for symptoms of nasal congestion •Short and long-acting antihistamines. Within 21 days prior to the planned date of viral challenge: •Chronically used medications, vitamins or dietary supplements, including any medication known to

Prohibited medication	Washout
	be moderate/potent inducers or inhibitors of CYP450 enzyme.

Any concomitant medication required for the participant's welfare may be given by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication and the reason for its use are recorded appropriately in the source notes to permit their transfer to the clinical database.

The use of paracetamol and/or other allowed medications is permissible within 7 days before the date of first dosing with IMP/viral challenge (whichever occurs first) at PI discretion. During the study periods, the Investigator may permit a limited amount of paracetamol (no more than 4 g per day i.e. maximum daily dose) or topical medication, as clinically required for the treatment of headache or any other pain. Other medication to treat AEs may be prescribed if required.

Medications which are permitted throughout the study are shown in Table 4 below:

Table 4 – Permitted Medication

Permitted medication	Time period
Paracetamol	Maximum 4g daily throughout the study duration at PI discretion.
Oral contraceptives	Allowed at any time during the study.
Prescription and non-prescription medications, including vitamins or herbal and dietary supplements, not listed in prohibited medications are subject to approval by the PI.	

6.6. Dose Modification

Modification to the Palivizumab dose from 8mg/kg to 15mg/kg may be required for Part 2 of the study.
Dose selection for Part 2 will be made by the Sponsor based on a review of the PK data obtained from at least 6 participants dosed with 8mg/kg of Palivizumab in Part 1; and a confirmation of no safety or tolerability concerns from the Safety Data Review Meeting as described in Section 10.1.5.
The PK assessment up to and including Day 12 exposure will be used as a decision information for the dose for Part 2. PK exposure data from at least 5 out of 6 participants is required for dose decision making with a projected exposure of ≥40 µg/mL on Day 12.

7. Discontinuation of Study Intervention/Withdrawal

7.1. Participant Withdrawal

A participant may withdraw their consent to participate in the study at any time, for any reason, without prejudice to his/her future medical care. Participants may decline to give a reason for their withdrawal. Additionally, the PI 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 as described in Section 2.3.1

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.

7.2. 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.

- 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.

7.2.1. 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. For participant rescreening refer to Section 5.4

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a follow-up letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.4. 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.

7.5. Stopping Rules

The PI and the SME will perform safety reviews on available clinical and virology data as appropriate during the quarantine period.

Three clinical scenarios relating to the incidence of SAEs/SUSAR during the study and the procedures that should be performed in each case are presented in Table 5.

Table 5 – Study Stopping Rules

Status	Criterion	Procedure
1	A report has been received of one (or more) SUSAR in anyone (or more) participant(s).	If such a status occurs at any point during the study, then further administration of Palivizumab will not take place. The PI and the SME will review the data and make decisions on whether it is appropriate to recommence dosing (via a substantial amendment, if indicated) or terminate the study.
2	No SUSAR have been reported but an overall pattern of clinical changes or symptoms exists, attributed to the IMP, which may appear minor or moderate in terms of individual AEs, but which collectively represent a concern for safety.	If such a status occurs at any point during the study, then further administration of IMP will not take place. The PI and the SME will review the data and make a decision on whether it is appropriate to recommence dosing (via a substantial amendment, if indicated) or terminate the study.
3	Unexpected virus-related SAE or Unexpected virus-related AEs of clinical concern have been reported following Human Viral Challenge. *Expectedness will be assessed by referring to the challenge virus dossier	If such a status occurs at any point during the study, then the PI and the SME will review the data and make a decision based on expectedness* of the viral event. If the event is unexpected, further administration of the virus will not take place. The PI and the SME will review the data and make a decision on whether it is appropriate to recommence inoculation (via a substantial amendment, if indicated) or terminate the study.

In any event, participant follow-up should continue until resolution or stabilisation of AEs and final follow-up on Day 28 (± 3 days).

8. Study Assessments and Procedures

Study procedures and their timing are summarised in the SoA. Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. Immediate safety concerns should be discussed with the Sponsor upon occurrence or awareness to determine if the participant should continue or discontinue study intervention

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to document eligibility or record the reasons for screening failure, as applicable.

For all study assessments, the value obtained nearest to dosing will be used as the baseline measure for assessments, unless stated otherwise.

Procedures conducted as part of the hVIVO Generic Screening process and obtained before signing of the study specific Informed Consent Form (ICF) may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Where applicable, unless otherwise stated, normal ranges will be identified in the Investigator Trial Master File (TMF).

8.1. Medical and Medication History

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

8.2. Demographics

Demographic data will be recorded at screening.

8.3. Height, Weight and Body Mass Index (BMI)

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

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

8.4. Complete Physical Examination

A complete physical examination to include a full systemic assessment.

8.5. Direct Physical Examination

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.

Following viral challenge, URT and LRT symptoms (as described above) will be expected and presumed to represent virus infection consequent to viral challenge and will not be additionally captured as AEs unless they meet the definition of an AE, and are deemed to be clinically significant (in the opinion of the Investigator) to be classed as AEs.

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

8.6. Vital Signs

Vital signs assessments will be recorded as follows:

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

In the event of a participant having an unexpected abnormal or out of normal range result, the assessment may be repeated after at least 2 minutes to exclude a technical fault and confirm the original reading. The assessment may then be repeated at the PI's discretion and in accordance with hVIVO's SOPs.

Study specific normal ranges are provided in Appendix 4. If a result is out of the normal range and meets the criteria for an AE, the severity of the AE will be guided by the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007.

Deterioration in a vital sign (compared to baseline) should only be reported as an AE if the deterioration fulfils the criteria for an AE. If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated vital sign will be considered as additional information

8.7. Tympanic Temperature

The study specific normal range for tympanic temperature is detailed in Appendix 4.The severity of out of normal range values will be assigned using the DMID toxicity scale as a guide.

Temperature may be more frequently monitored in quarantine if appropriate.

Following viral challenge, pyrexia will be expected and presumed to represent virus infection consequent to viral challenge and will not be additionally captured as an AE unless it meets the definition of an AE, and is deemed to be clinically significant (in the opinion of the Investigator) to be classed as an AE.

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

Febrile illness (FI) is defined as any occurrence of temperature ≥ 37.9 ^{o}C

8.8. Electrocardiogram

Study specific normal ranges are provided in Appendix 4.

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

Any changes from baseline during the study will be assessed for their clinical significance. Clinically significant changes will be reported as AEs. The PI or delegate will assess non-clinically significant changes to determine whether they should be recorded.

8.9. Spirometry

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

Spirometry should meet the ATS/ERS guidelines criteria(Miller et al. 2005). For FEV_1 and FVC, the highest value from a minimum of 3 technically satisfactory attempts will be considered. For FEV_1 and FVC the highest and the second highest value should not exceed more than 150 mL or 5% (whichever is greater). If the difference is larger, up to 8 technically acceptable measurements will be made with repeatability assessed after each additional attempt. If after 8 technically acceptable attempts the difference remains greater than 150 mL or 5% (whichever is greater) the highest values will be reported, and an operator comment will be made to the source data. FEV_1 and FVC will be assessed and reported as the highest values regardless of curve.

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

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

8.10. Peak expiratory flow (PEF)

All participants will self-test their PEF using portable, hand-held Peak Flow Meters (PFMs). The PEF self-test must be observed by quarantine staff when recorded during quarantine to ensure compliance and technique.

8.11. Forced oscillation technique (FOT)

Forced oscillation technique (FOT) is a versatile, non-invasive assessment of respiratory mechanics based on tidal breathing analysis. Airwaves of multiple frequencies (typically 5 to 30 Hz) are applied to the respiratory tract during relaxed breathing. The test involves participants breathing through a breathing handle in a seated position, wearing a nose-clip, with cheeks supported. Breathing is recorded for approximately 1 minute. During this time the instantaneous pressure-flow relationship, measured at the mouth at varying frequencies, are analysed in order to measure Respiratory Impedance (Zrs). Zrs is made up of an in-phase, termed resistance (Rrs) and out-phase, referred to as reactance (Xrs). Resistance at 5Hz penetrates the periphery of the lung, providing information of the entire respiratory tract. Resistance > 20Hz represents respiratory resistance of the proximal airways. Distal lung resistance can be calculated by

subtracting total airway resistance from proximal airway resistance (R5-R20). Xrs comprises of 2 elements that are dependent upon frequency. At higher frequencies (>20 Hz) Xrs is positive in sign and represents the inertive force needed to move air in the conducting airways. At low frequencies of 5 Hz (X5) is negative in sign and indicates the capacitance of the lung periphery. A minimum of 3 tests will be performed and the mean values reported. Testing will take approximately 5 minutes

FOT is an exploratory measure of small airway lung function and may be measured on a subset of volunteers.

8.12. Patient Health Questionnaire (PHQ-9) and Generalised Anxiety Disorder (GAD-7) Questionnaire

PHQ-9 and GAD-7 questionnaire will be used at the discretion of the investigator at screening and/or quarantine admission to assess participants' eligibility in terms of ability to tolerate isolation in the quarantine unit.

8.13. Participant Symptom Diary Card

Participants will report and assess the severity of any challenge virus-related signs and symptoms three times/day during quarantine, at the same time each day (± 1 hour), using the hVIVO Symptom Diary Card. This information will be collected using a paper form.

The following symptoms in the 13-item symptom questionnaire will be graded on a scale of 0-3 (grade 0: No symptoms; grade 1: just noticeable; grade 2: clearly bothersome from time to time but does not interfere with me doing my normal daily activities; grade 3: Quite bothersome most or all of the time, and it stops me participating in activities):Shortness of Breath and Wheeze have an additional grade 4: Symptoms at rest

- Runny nose
- Stuffy nose
- Sneezing
- Sore throat
- Earache
- Malaise/tiredness
- Headache
- Muscle and/or joint ache
- Chilliness/Feverishness
- Cough
- Chest tightness
- Shortness of breath
- Wheeze

Additional to the categorical symptom diary card, a Visual Analogue Scale dairy card using a 100mm scale, with the same symptoms, will be completed by the participants.

The Investigator will assess and review challenge virus-related symptoms that are recorded on the diary card following each scheduled completion.

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

Participant cold perception questions

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

1. Do you have a cold: Yes/No

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

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

8.14. Nasal Discharge Collection from Paper Tissues

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

A daily 24-hour collection will take place throughout the quarantine period. Distribution of paper tissues and bags will start on Day -2, with the first collection on Day -1. Thereafter distribution and collection of tissues will occur at 08:00h (± 1 hour). Tissues will be handed out daily and collection will occur until the discharge from quarantine.

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

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

- 24-hour nasal discharge weight.
- The number of paper tissue used for nasal discharge over 24-hour period.

8.15. Alcohol Breath Testing

Breath alcohol testing will be conducted to determine compliance with the study alcohol restrictions. Additional tests may be conducted for assessing eligibility at the discretion of the investigator. Results will be recorded in the source documents.

8.16. Urinalysis

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

Urinalysis will be performed to evaluate the parameters described in Appendix 2.

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

Urine safety analysis values will be evaluated by the Investigator for clinical relevance. Those deemed to be clinically significant will be reported as AEs.

8.17. Urine Drugs of Abuse and Nicotine Test

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

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

8.18. Pregnancy Test

Female participants of childbearing potential are to have a urine pregnancy test at screening. Participants will only be enrolled if the pregnancy test is negative.

Note: Pregnancy test must be performed even if the participant is menstruating at the time of the study visit.

Blood samples will be tested for serum FSH in post-menopausal women only.

8.19. Blood Samples

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

8.19.1. Safety Blood Samples

Appendix 2 describes the safety blood tests that will be performed including, but not limited to, haematology, biochemistry and cardiac enzymes. Additional safety assessments (e.g. coagulation) will be conducted at the discretion of the PI/Investigator, as required

8.19.2. Challenge Virus Serology Samples

Participants in Part 2 must be sero-suitable to take part in the study; i.e. he/she must have no or low pre-existing serum levels of antibodies specific to the Challenge Virus. This antibody titre cut-off for sero-suitability will be described in the AP.

Serum levels of pre-existing RSV specific antibodies to the Challenge Virus will be determined as described in the AP.

8.19.3. Pharmacokinetic Blood Samples

Blood (plasma) samples for the evaluation of PK parameters of Palivizumab will be collected as outlined in the PK Sampling Schedules below:

Part 1 PK Sampling Schedule:

Before the start of infusion; at end of infusion,15min, and 0.5, 1, 4, 8, and 12 h after infusion; and at 1, 2, 3, 7, 12 days after infusion.

The allowable time windows for the sampling are as follows:

- ± 5 minutes from the scheduled time for time points ≤ 1 hour from infusion;
- ± 15 minutes from the scheduled time for time points > 1 hour from infusion, with NOTE below:
    - 1 day timepoint: +/- 1 hour window
    - 2 days timepoint: +/- 2 hours window
    - 3 days timepoint: +/- 2 hours window
    - 7 days timepoint: +/- 1 day window
    - 12 days timepoint: +/- 3 hours window
- There is no time window requirement for the pre-infusion sample. The pre-infusion PK sample must be taken on the same day prior to infusion.

Part 2 PK Sampling Schedule:

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.

The allowable time windows for the sampling are as follows:

- ± 5 minutes from the scheduled time for time points ≤ 1 hour from infusion;
- ± 15 minutes from the scheduled time for time points > 1 hour from infusion, with NOTE below:
    - 1 day timepoint: +/- 1 hour window
    - 2 days timepoint: +/- 2 hours window
    - 3 days timepoint: +/- 2 hours window
    - 7 days timepoint: +/- 2 hours window
    - 13 days timepoint: +/- 2 hours window
    - 21 days timepoint: +/- 2 days window
    - 29 days timepoint: +/- 3 days window (and with at least 5 days after the previous PK sampling timepoint)

- There is no time window requirement for the pre-infusion sample. The pre-infusion PK sample must be taken on the same day prior to infusion.

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

8.19.4. Anti-drug Antibody Blood Samples

Blood (plasma) samples for the evaluation of anti-Palivizumab antibodies will be collected as outlined in the ADA Sampling Schedules bellow:

Part 1 ADA Sampling Schedule:

Before the infusion, and at 7 and 12 days after infusion.

The allowable time windows for the sampling are as follows:

- 7 days timepoint: +/- 1 day window
- 12 days timepoint: +/- 3 hours window

Part 2 ADA Sampling Schedule:

Before the infusion, and at 7, 13 and 29 days after infusion. The allowable time windows for the sampling are as follows:

- 7 days timepoint: +/- 2 hours window
- 13 days timepoint: +/- 2 hours window
- 29 days timepoint; +/- 3 days window

There is no time window requirement for the pre-infusion sample.

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

8.19.5. Blood Samples for Exploratory Research

Remaining aliquots of blood may be stored and used for exploratory immunology analysis related to viral infection and the response to treatment. These analyses may include but are not limited to:

- immunology assays related to baseline immunity and response to infection with RSV
- Immune assays related to Palivizumab (e.g. IgG anti-F ELISA, PCA)

8.20. Upper Respiratory Samples

The following exploratory upper respiratory sampling procedures will be performed during the study:

- Nasopharyngeal FLOQ swab or nasal wash, as appropriate

8.20.1. Nasal samples

Nasopharyngeal FLoQ swabs or nasal wash, as appropriate, will be performed to collect samples of nasopharyngeal cells and epithelial lining fluid for:

- Respiratory Pathogen Screen
- RSV discharge test
- Viral loads
- Exploratory purposes

Tolerance of the procedure may be determined at the screening visit.

8.20.1.1. Viral Load

Viral load will be determined by quantitative reverse transcription polymerase chain reaction (qRT-PCR) and/or a viral culture assay to investigate the following parameters:

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

8.20.1.2. Respiratory Pathogen Screen

On entry to quarantine, a nasopharyngeal swab or nasal wash will be collected and tested to detect the presence of a set of respiratory pathogens, including Covid-19, that could potentially contraindicate a participant's participation in the study. The methodology to be used to conduct the respiratory virus screen will be documented in the Analytical Plan. Additional test may be conducted if the results from the first test were invalid to support study eligibility prior to virus inoculation, or if a community acquired infection is suspected during quarantine.

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

8.20.1.3. RSV discharge test

A PCR based test will be used to determine the presence of RSV in a nasopharyngeal swab or nasal wash sample taken prior to discharge from the Quarantine Unit on Day 12 (and subsequent days if, at the discretion of the PI, an extended quarantine stay is required due to the PCR test result and/or the presence of clinical symptoms).

8.20.1.4. Exploratory purposes

Remaining aliquots of nasal samples may be stored and used for exploratory immunology analysis related to viral infection and the response to treatment. These analyses may include but are not limited to:

- immunology assays related to baseline immunity and response to infection with RSV
- Immune assays related to Palivizumab (e.g. IgG anti-F ELISA, PCA)

8.21. Recording of Adverse Events and Serious Adverse Events

The Investigator (PI) is responsible for ensuring that all AEs, SAEs and pregnancies are identified, evaluated, recorded and reported in a timely manner as per Regulatory requirements and hVIVO's SOPs. The Investigator's responsibility is to ensure that the medical management of AEs, SAEs and pregnancy events (participant/partner of male participant) is delegated to adequately trained, competent Investigator Site staff.

The Sponsor of the study will also perform an evaluation of seriousness, causality and expectedness of all SAEs.

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 10.3.

8.21.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs will be collected from the signing of the ICF until the last Follow-up Visit at the time points specified in the SoA (Section 1.3).

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the sponsor.

8.21.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.21.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. Additional Information/clarification may be required to ensure accurate completion of safety reports. The follow up reports should include a detailed Investigator's clinical assessment. All AEs/SAEs, will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3.

8.21.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator (PI) to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The following reporting process will be followed:

- PI will send SAE/pregnancy forms to mAbxience PV (sponsor) within 24 hours of becoming aware of the event
- mAbxience PV will assess expectedness to determine if the SAE requires expedited reporting
- mAbxience PV will send query to the PI if additional information is needed
- mAbxience PV will report the case to the Medicines and Healthcare Regulatory Agency (MHRA) via the EudraVigilance Database Management System EVWEB (or alternatively using MHRA eSUSAR tool)

- PI (or hVIVO) will report SUSAR and other relevant safety information to the Ethics Committee in accordance with REC guidelines.

The sponsor has a legal responsibility to ensure that the local regulatory authority and other regulatory agencies duly informed about the safety of a study intervention under clinical investigation. The sponsor ensures compliance with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

An Investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and will notify the IRB/IEC, if appropriate according to local requirements.

Further information on regulatory reporting requirements is provided in Appendix 10.3.

8.21.5. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected from study specific informed consent and until the last study assessment as outlined in the SoA. If a pregnancy is reported, the Investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 10.3.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.21.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.22. Treatment of Overdose

For this study, any dose of any drug administered as part of the study greater than the dose prescribed by the protocol will be considered an overdose.

In the event of an overdose. the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities associated with overdose and participants will be clinically followed up until the AE has resolved.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

The Sponsor is responsible for notifying the MHRA and REC of the potential serious breach within 7 days of becoming aware of it.

8.23. Pharmacokinetics

Blood (plasma) samples for the evaluation of PK parameters of Palivizumab will be collected as outlined in section 8.19.3.

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

Drug concentration information that may unblind the study will not be reported to investigative site or blinded personnel until the study has been unblinded.

8.24. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9. Statistical Considerations

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

Part 1 data analysis will be reported after completion of Part 1, and based on these results, Part 2 of the study will commence.

9.1. Statistical Hypotheses

There are no statistical hypotheses for Part 1. For Part 2, the main hypothesis is that Intravenous (IV) treatment with Palivizumab will have a prophylactic effect on RSV disease, that will translate to a lower infection rate and/or lower clinical symptomatology and/or lower viral titres compared to placebo.

Considering that the objectives of Part 2 are not for demonstration of statistically significant differences between groups, formal hypothesis testing will be performed for the main endpoints, as described in Section 1.1.6. All tests will be two-sided, using a type-one error probability of 0.05. p-values between 0.05 and 0.10 will be considered as indicative of a trend. As this is an exploratory study, no adjustment for multiple testing will be performed.

9.2. Sample Size Determination

9.2.1. Part 1 sample size

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.

9.2.2. Part 2 challenge study sample size

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 participants (25 Palivizumab treated participants and 25 placebo participants) in Part 2 of the study was calculated based on the assumptions of an infection rate of 73.7%, (infection rate obtained from placebo group participants from 7 studies totalling 216 RSV challenged participants, with 160 infected), 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*Log_{10} 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 participants 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 participants 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 participants	0.522	0.601	0.660	0.729	***0.800***	0.843	0.886
Power, 10 % two sided with 25 participants	0.644	0.716	0.781	0.835	0.881	0.916	0.940

9.3. Populations for Analyses

The following populations are defined:

Part 1

Population	Description
Enrolled	All participants who signed the informed consent.
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.
Safety Analysis Set	All participants assigned to study intervention and who take a dose of study treatment.
PK Analysis	The PK Analysis set is defined as all participants with at least one post-dose PK result.

Part 2

Population	Description
Enrolled	All participants who signed the informed consent and randomised to study treatment.
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.
Safety Analysis	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.
PK Analysis	The PK Analysis set is defined as all participants with at least one post-dose PK result.

The primary analysis will be on the evaluable population. The safety evaluation will be performed on the Safety Analysis population.

9.3.1. Subgroup Analysis

A 'Laboratory confirmed infected' subgroup will be identified and certain pre-specified analyses (to be documented in the SAP) will also be performed.

9.4. Interim Analysis

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

Interim analyses in Part 2 will only assess the Placebo group infectivity, that impacts powering assumptions.

9.5. Sequence of Analysis

A specific statistician (name 'unblinded statistician' in the remainder of this document) will be dedicated to performing all unblinded analyses conducted before the final database lock and unblinding. As soon as the first unblinded analysis, the unblinded statistician will remain independent from the project to maintain the study team blinded.

Part 1

- The analysis of the PK data obtained from Part 1 of the study, confirming the dose to be used in Part 2 will be conducted as soon as part 1 will be completed. The PK assessment to progress from Part 1 into Part 2 is as described in Section 9.6.10

Part 2

- 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.

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.

- The main analysis will be performed when efficacy (qRT-PCR and categorical symptom scores) clean data up to discharge from quarantine (Day 12) are available from all participants. In addition, PK data that may become available at that time might be analysed as well. The unblinded statistician will be unblinded for these analyses (i.e., will have access to the individual participant treatment assignment). The remaining study personnel will remain blinded (i.e., will not have access to the individual participant treatment assignment) until study end and database lock. No individual listings are expected to be required until End of Study (EOS) and the Investigator will not have access to the treatment allocation up to study end and database lock. This analysis will be considered as final for key efficacy endpoints.
- A final EoS analysis will be performed when all endpoint data (safety and efficacy) up to study end (Day 28) are available and locked. 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. Individual listings will only be provided at this stage.

The final CSR will contain at least the final analyses of endpoints. If the data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed. These analyses will be documented separately to the CSR and will be made available to the Sponsor and Investigators at that time.

9.6. Statistical Analysis

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

9.6.1. Statistical Analysis Plan

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

The detailed SAP will be developed by Venn Life Sciences and approved by the Sponsor prior to any look at unblinded data. The SAP will give a more detailed description of the report presentations to be produced for Parts 1 and 2 of the study, respectively, expanding on the protocol specified analysis. Any deviation(s) from the original statistical plan should be described and justified in an amendment to the protocol and/or SAP as appropriate and referenced also in the final clinical study report (CSR).

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

9.6.2. General statistical methods

9.6.2.1. Descriptive statistics

Continuous variables will be summarised using the following statistics: number of available data, number of missing values, mean (and/or geometric mean where applicable), standard deviation, median, Q1, Q3, minimum and maximum values. When relevant, confidence intervals will be computed for the mean or the median.

Categorical variables will be summarised using number of available data, number of missing values, frequency counts for each category and corresponding percentage. Percentages will be calculated using the number of available data as the denominator (i.e. not including missing values). When relevant, confidence intervals will be computed.

9.6.2.2. Inferential statistics and significance testing

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, analysis of covariance, or linear mixed-models for repeated measures 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. Details on the method used for each endpoint will be provided in

the SAP. Methods for checking statistical model assumptions and alternative methods of analysis if the assumptions are not fulfilled will be described in the SAP.

For categorical variables, differences in absolute frequency and/or relative risks will be presented, with their 95% two-sided CIs will be presented. Except otherwise specified in the SAP, the Chi-square test will be used to compare frequencies between groups.

As the study is explorative by nature, there will be no attempt to adjust for the multiplicity of endpoints.

9.6.3. Participant accountability

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

9.6.4. Protocol deviations

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

9.6.5. Demographic and baseline characteristics

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

9.6.6. Compliance to study treatment

Compliance with study drug will be computed for each patient as proportion of prescribed study drug actually taken.

9.6.7. Efficacy Endpoint(s)

Endpoints	Planned Inferential Analysis
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.	t-test if assumptions valid
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.	
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.	

Endpoints	Planned Inferential Analysis
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.	MMRM for repeated measures, if underlying assumptions valid
Total weight of nasal discharge produced starting one day post viral challenge (Day +1) up to the end of quarantine.	t-test if assumptions valid
Total number of tissues used by participants starting one day post viral challenge (Day +1) up to the end of quarantine.	
Occurrence of 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.	Chi-square test
Occurrence of 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	
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.	t-test if assumptions valid
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.	t-test if assumptions valid
Incidence of symptomatic RSV infection, as defined by: o Incidence of infection, and o At least one grade 2 symptom from one or more respiratory categories from the participant symptom diary card.	Chi-square test (on both the composite and each component)
Number of days with symptoms of grade 2 or more, starting one day post viral challenge (Day +1) up to the end of quarantine.	-test if assumptions valid
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.	-test if assumptions valid

9.6.8. Tertiary/exploratory efficacy endpoint(s)

No formal statistical testing will be conducted for tertiary and exploratory endpoints. Only the descriptive statistics, as presented in Section 9.6.2.1 will be computed.

9.6.9. Safety Analyse(s)

AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, and treatment group for the number of AEs reported and the number and percentage of patients reporting each AE.

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.

Other safety data, including laboratory evaluations (biochemistry, haematology, coagulation (if required), cardiac enzymes and urine analysis)), vital signs assessments, physical examinations, 12-lead ECG and Spirometry will be summarized by time of collection and by treatment group. In addition, change from Baseline will be summarized for vital signs and clinical laboratory results.

The frequency of patients with abnormal safety laboratory results will be tabulated by treatment.

9.6.10. Other Analyses

The analysis of the PK data obtained from Part 1 of the study, confirming the dose to be used in Part 2 will be conducted as soon as part 1 will be completed. The PK assessment up to and including Day 12 exposure will be used as a decision information for the dose for Part 2. PK exposure data from at least 5 out of 6 participants is required for dose decision making with a projected exposure of ≥40 µg/mL on Day 12.

The following pharmacokinetic endpoints will be presented by treatment group:

- Serum PK parameters of Palivizumab following dose administration in healthy adult participants inoculated with RSV-A Memphis 37b will be defined in the PK Analysis Plan.

PK parameters will be calculated using non-compartmental methods. Parameters will be summarised descriptively. Exploratory PKPD modelling may be performed to inform the exposure response for subsequent studies.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

When historical screening data collected through the hVIVO generic screening process is used for screening, the study specific ICF will be obtained at quarantine admission (Day -3/-2) from each participant before any study specific procedures are performed.

Potential participants will typically be sent a copy of the ICF when their Screening Visit/Quarantine admission visit (as applicable) is arranged and at least a day prior to the visit and will be encouraged to read it prior to their appointment. Upon arrival at the Screening Visit/Quarantine admission visit (as applicable), the ICF is discussed by the Investigator, and they will be given the opportunity to ask any questions and may take the information sheet away to consider their participation.

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

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

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

The ICF will contain a separate section that addresses the use of samples for future research. The Investigator or authorised designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

The decision on the dose level (8mg/kg or 15mg/kg) to be used for Part 2 of the study will be based on the outcome of PK data from Part 1 and a review of the safety and tolerability of the 8mg/kg dose level.

A Safety Data Review meeting between the Sponsor and the Investigator is required prior to Part 2 for a formal assessment of all safety data up to and including Day 12. The meeting will at a minimum consist of the Sponsor’s Medical Monitor and the PI.

Clinical safety data required for review are 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.

10.1.6. Dissemination of Clinical Study Data

The key design elements of this Protocol will be posted on publicly accessible registers, such as ClinicalTrials.gov. Where required, protocol summaries will also be posted on national or regional clinical trial registers or databases (e.g., EudraCT database) in compliance with the applicable regulations.

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

The PI/Investigator shall provide assurance to participants that their confidentiality will be maintained hVIVO have a legal obligation to protect at all times the confidentiality of participant personal data from the point of capture, through processing, dissemination in line with consent from the participant and to its final disposition.

10.1.7. Data Quality Assurance

Participant data will be collected at site using paper source casebooks which will then be data entered into the electronic case report form (eCRF) database unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (remote or on-site monitoring) are provided in the Monitoring Plan.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator during the retention period as agreed with the sponsor and as required by local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Source Data Agreement.

10.1.9. Study Discontinuation

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

If the study is suspended or terminated for safety reason(s), the Sponsor will promptly inform the PI, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action.

The PI/Investigator is responsible for promptly informing the REC and providing the reason(s) for the suspension or termination of the study.

If the study is prematurely terminated, all study data must be returned to the Sponsor. In addition, the site must conduct final disposition of all unused IMPs in accordance with the Sponsor's procedures for the study.

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

10.1.10. Publication Policy

By signing the study protocol, the PI agrees that the results of this study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor.

If necessary, the authorities will be notified of the PI's name, address, qualifications, and extent of involvement. In order to allow the use of the information derived from this clinical study, the PI understands that he has an obligation to provide complete test results and all data developed during this study to the Sponsor.

If the study is to be published, the Sponsor and hVIVO may jointly prepare and co-author manuscript(s) that could result from the clinical trial. In the case the Sponsor acts as fully responsible for the publication, the Sponsor agrees to allow the PI time to review all manuscripts and abstracts prior to submission for publication. mAbxience reserves the right to include the report of this study in any regulatory documentation or submission or in any informational materials. The Sponsor also reserves the right to delete any confidential information from any proposed manuscripts prior to submission for publication. Confirmation of study specific arrangements can be found in the clinical study agreement.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed The Doctor's Laboratory (TDL).
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy Testing

Table 6 - Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Haematology	Platelet Count. White blood cell (WBC) count (absolute) WBC differential: Neutrophils Lymphocyte Monocytes Eosinophils Basophils Red blood cell (RBC) count Reticulocyte count (% and absolute) Haemoglobin Haematocrit Mean corpuscular volume (MCV) Mean corpuscular haemoglobin (MCH) MCH concentration (MCHC).
Coagulation	Prothrombin Time (PT) Activated Partial Thromboplastin Time (APTT)
Biochemistry	Sodium Potassium Glucose (random) Albumin Chloride Bicarbonate Calcium Uric acid Total protein Creatinine Total, direct, and indirect bilirubin Inorganic phosphate Blood urea nitrogen C-reactive protein (CRP) Gamma glutamyl transferase Alkaline phosphatase (ALP)

Laboratory Assessments	Parameters
	Alanine transaminase (ALT) Lactate dehydrogenase (LDH) Aspartate transaminase (AST) Urea.
Thyroid function	Thyroid Stimulating Hormone (TSH) Thyroxine
Cardiac enzymes	Creatine Kinase (CK) CK-MB Troponin (T)
Routine 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)
Other screening/eligibility tests	Follicle stimulating hormone (FSH)* β-human chorionic gonadotrophin (β-hCG) Total cholesterol Thyroid function test [thyroid stimulating hormone (TSH), free thyroxine (T4)] Antibodies against HIV-1 and HIV-2 Hepatitis A immunoglobulin M (HepA) Hepatitis B surface antigen (HBsAg) Hepatitis C antibodies (HepC)

*Only for post-menopausal women

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Adverse Event

AE Definition
An AE is defined as any untoward medical occurrence in participants. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered

related to the investigational medicinal product, or for the purposes of Human Viral Challenge studies, the Challenge Virus.

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

Events NOT Meeting the AE Definition
• Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE. • Pre-existing disease or conditions present or detected prior to start of IMP or Challenge Virus inoculation administration that does not worsen (including screening findings such as abnormal laboratory results). • Hospitalisation for elective surgery, social and/or convenience admissions provided they are arranged before the start of IMP administration. • Over-administration of either the challenge virus, IMP or concomitant medication without any signs or symptoms. • An uncomplicated pregnancy or an induced elective abortion to terminate a pregnancy without medical reason. • Typical/normal viral symptoms on symptom diary cards.

10.3.2. Adverse Drug Reaction

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

'Response' in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

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

10.3.3. Unexpected Adverse (Drug) Reaction

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

(a) In the case of a product with a marketing authorisation, in the Summary of Product Characteristics for that product, which is applicable for this study

(b) In the case of any other investigational medicinal product, in the Investigator's Brochure relating to the trial in question', not applicable for this study.

For this study the option (a) is applicable.

10.3.4. Serious Adverse Event

SAE Definition
A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is an important medical event: • Important medical events' - some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered as 'serious' in accordance with the above definition.

- Medical judgement should be exercised in deciding whether an adverse event/reaction is serious. Important adverse events/reactions that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above occurring, should also be considered serious. Details of the SAE must be provided.

10.3.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is 'a serious adverse reaction, the nature and severity* of which is not consistent with the information about the medicinal product in question, as defined in the Summary of Product Characteristics (SmPC), included in this clinical trial application package.

Expectedness of adverse events will be determined by the sponsor. The Reference Safety Information (RSI) document for this study is the Summary of Product Characteristics (SmPC), section 4.8.

Any changes to the referenced safety information will be deemed as a change to the risk/benefit profile and will require a substantial amendment to be submitted to the MHRA. This amendment must be approved before the changes are implemented in the study.

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

10.3.6. Recording, Assessment and Follow-up of AE and/or SAE

10.3.6.1. AE and SAE Recording

All AEs and SAEs will be collected from the date of signed written informed consent until study completion/final study contact or until the resolution of the AE. AEs will be fully recorded in the source documents as they are reported whether spontaneously volunteered by a participant or in response to questioning about wellbeing at each face to face study visit and during telephone calls. Enquiries about AEs should cover the period between the previous and current visit.

The following are examples of open ended, non-leading questions that may be used to obtain this information:

- How are you feeling?
- Have you had any medical problems since your last visit/assessment?
- Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?

Following the reporting of AEs and concomitant medication, the Investigator should assess the participant's eligibility to continue in the study.

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

- Description of events (if the event consists of a cluster of signs and symptoms, a diagnosis should be recorded)
- Seriousness
- Severity (or grade)

- Onset date and time
- Frequency
- Date and time of resolution (or 'continuing' if unresolved)
- Action taken
- Concomitant medication
- Clinical outcome
- Relationship or causality (IMP/Challenge Virus/ study procedures/ concomitant medication/other).

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

If an AE is not resolved at the end of the study, the AE should be followed until it has resolved or (in the case of pregnancy) the pregnancy has been terminated (including spontaneous abortion), resulted in a birth, or a decision has been made by the Sponsor that no further follow-up is required.

Even if the AE or SAE is assessed by the PI as not reasonably attributable to the challenge virus, its occurrence must be fully documented in the source notes

10.3.6.2. Assessment

Description

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

Onset and end

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

Assessment
Challenge Virus Symptoms The Investigator will assess and review Challenge Virus related symptoms recorded in participants' hVIVO Symptom Diary Cards. Symptoms greater than Grade 0 will be expected and presumed to represent virus infection consequent to Viral Challenge, and will not be additionally captured as AEs unless they meet the definition of an AE, and are deemed to be clinically significant (in the opinion of the Investigator) to be classed as AEs. Following Viral Challenge all unexpected (in the opinion of the Investigator) symptoms post inoculation will be captured as AEs, along with all other occurrences that meet the criteria for an AE.
Physical Examination Any clinically significant change in complete physical examination findings during the study will be documented as an AE.
Direct Physical Examination Following Viral Challenge, upper and lower respiratory symptoms (nasal discharge, otitis, pharyngitis, sinus tenderness, new wheezes, rales and rhonchi) will be expected and presumed to represent virus

infection consequent to Viral Challenge, and will not be additionally captured as AEs unless they meet the definition of an AE, and are deemed to be clinically significant (in the opinion of the Investigator) to be classed as AEs.

Vital Signs

Deterioration in a vital sign (compared to baseline) should only be reported as an AE if the deterioration fulfils the criteria for an AE. If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated vital sign will be considered as additional information.

Temperature

Following Viral Challenge, pyrexia will be expected and presumed to represent virus infection consequent to Viral Challenge, and will not be additionally captured as an AE unless it meets the definition of an AE, and is deemed to be clinically significant (in the opinion of the Investigator) to be classed as an AE.

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

Spirometry

A 15% drop in a spirometry value (compared to baseline) confirmed by a repeat on the same day, will be a Grade 1 (mild) AE. The PI/Investigator will use his/her clinical judgement to assign severity grades above Grade 1, based on evaluation of clinical signs and symptoms. If the repeated value has returned to normal an AE will not be raised.

Laboratory Values

Deterioration in a laboratory value (compared to baseline) should only be reported as an AE if the deterioration fulfils the criteria for an AE. If deterioration in a laboratory result is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result will be considered as additional information.

The Investigator and/or SME will judge whether abnormal laboratory values are clinically significant or not clinically significant, and record this in the source document. This entry should be signed and dated by the relevant Investigator. Laboratory abnormalities detected at screening will be considered as part of the medical history and will not be reported as AEs

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

C-reactive Protein

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

10.3.6.3. Assessment of Intensity

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

The PI will use the [grading scale for AEs] as a reference when collecting, reporting and clarifying database queries of AEs, SAEs and ARs.

The severity of an AE that does not appear in the [grading scale for AEs] should be determined according to the definitions in Table 7

Table 7 – Classification of Adverse Event Severity

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

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. It is important to distinguish between serious and severe AEs. An AE of severe intensity needs not necessarily be considered serious. For example, a migraine headache that incapacitates a participant for many hours may be severe, whereas a stroke that results in a limited degree of disability may be considered mild, but should be reported as a SAE.

10.3.6.4. Frequency

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

- Single
- Intermittent
- Continuous

10.3.6.5. Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The Investigator will also reference the Reference Safety Information (RSI) section in the SmPC, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Sponsor's Pharmacovigilance provider. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- The relationship of an AE to the IMP will be categorised as shown in Table 8:

Table 8- Classification of Adverse Event Relationship

Classification	Definition
Not related	The AE is related to an aetiology other than the IMP (the alternative aetiology must be documented in the participant's medical record).
Unlikely to be related	The AE is unlikely to be related to the IMP and likely to be related to factors other than IMP.
Possibly related	There is an association between the AE and the administration of the IMP, and there is a plausible mechanism for the AE to be related to the IMP, but there may also be alternative aetiology, such as characteristics of the participant's clinical status or underlying disease.
Probably related	A reasonable temporal sequence of the AE and the IMP administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the AE with the IMP seems likely.
Definitely related	A definite causal relationship exists between the AE and the administration of the IMP, and other conditions do not appear to explain the AE.

Unless an AE is 'definitely related' to the IMP, a causal relationship to one of the following should be considered, and full details provided on the AE reporting form as appropriate.

- Challenge Virus
- Study procedures
- Concomitant medication
- Other

10.3.6.6. Action Taken

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

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

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

10.3.6.7. Outcome

An AE should be followed until the Investigator has determined and recorded the outcome or an alternative explanation. The outcome should be classified according to the categories shown in Table 9.

Table 9 - Classification of Adverse Event Outcome

Classification	Definition
Resolved	Resolution of the AE with **no** residual signs or symptoms
Resolved with sequelae	Resolution of the AE with residual signs or symptoms
Ongoing	Either incomplete improvement or no improvement of the AE, such that it remains on-going
Fatal	Outcome of the AE was death. 'Fatal' should be used when death was at least possibly related to the AE.
Unknown (e.g. Lost to follow-up)	Outcome of the AE is not known (e.g. the participant is lost to follow-up).

10.3.6.8. Follow-up

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

- Resolved (return to normal or baseline values), or
- Stabilised, or

- Judged by the PI/Investigator to be no longer clinically significant, or
- An alternative explanation has been provided.

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

10.3.7. Reporting of SAEs

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

Prompt notification of SAEs by the Investigator to the Sponsor is essential so that the Sponsor can meet its regulatory reporting obligations for the study. If the Investigator does not have all of the details regarding the SAE he/she will not wait until this information becomes available before making the initial report to Sponsor. Contact details are detailed in Table 10.

Notification should be made:

- In a detailed written SAE form report within 24 hours of the Investigator becoming aware of the event.

All reports should be directed to the pharmacovigilance mailbox. The Investigator at the site is responsible for ensuring that a member of the Sponsor study team is made aware of any SAE reports that have been transmitted.

Table 10 - Contact Details for Reporting SAEs

Contact	Details
Pharmacovigilance reporting email	pharmacovigilance@mabxience.com
Pharmacovigilance fax number reporting	0034 917711590
SAE e-mail address:	pharmacovigilance@mabxience.com

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

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

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

The Investigator will also provide additional information, including a copy of the following documents (where applicable):

- Copies of test results, as available
- Hospital discharge summary (as soon as it is available to the PI)
- Autopsy report (as soon as it is available to the PI).

The Investigator must report SAEs/SUSARs to the relevant REC in accordance with applicable regulatory requirements and within the relevant timelines.

The REC will be sent annual safety updates in order to facilitate their continuing review of the study.

10.3.8. Reporting of SUSARs

The Sponsor is responsible for assessing SUSARs, unblinding potential SUSARs, and reporting SUSARs to the MHRA.

The Sponsor shall ensure that all relevant information about a SUSAR that occurs during the course of a clinical trial in the UK and is fatal or life threatening, is reported as soon as possible to the MHRA. This needs to be done within 7 calendar days after the Sponsor became aware of the event. Any additional relevant information should be sent within 8 days of the first report being sent.

The Sponsor shall ensure that a SUSAR which is not fatal or life-threatening is reported as soon as possible and in any event within 15 calendar days after the Sponsor became aware of the event.

10.3.9. Adverse Reactions to non-IMPs

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

10.3.10. Post-study AEs and SAEs

All SAEs that occur during the [specify period] time period must be reported by the Investigator to the SME as soon as possible, in accordance with hVIVO's SOPs, and at the latest within 24 hours of becoming aware of the event.

10.3.11. Pregnancy

If a female participant or partner of a male participant becomes pregnant during [specify time period], this must be reported by the Investigator to the medical monitor and Study Monitor by telephone as soon as possible, in accordance with hVIVO's SOPs, and at the latest within 24 hours of becoming aware of the event.

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

Participants will be advised to contact their GP or a specialist, as appropriate.

Consent for follow-up of the pregnancy and pregnancy outcome will be sought from the pregnant study participant or the pregnant partner of the male study participant as applicable. Consent for follow-up will be documented on an hVIVO Pregnancy Follow-up ICF.

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

- A complete evaluation will be documented in the source data to permit transfer to the clinical database.
- An emergency request (Section 6.3) to break the blind for the appropriate study participant to ensure that further care can be based on the actual identity of the study treatment that the participant received.
- hVIVO will maintain contact with the participant for a protracted period of time, but certainly until after the birth, in order to assess for outcomes that may be reportable as related AEs, and for reporting to the Sponsor as appropriate.
- hVIVO in consultation with the participant will keep the participant's GP informed.
- All cases of foetal drug exposure via the parent as a study participant will be reported to the Sponsor and the REC.

10.4. Appendix 4: Normal Ranges

Vital Signs

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

ECG

ECG Parameters	Lower limit	Higher limit	Units
HR	50	100	bpm
QRS	60	120	ms
PR interval	120	220	ms
QT	320	450	ms
QTc	Normal for females is < 470		ms
	Normal for males is < 450		
QTcF	320	450	ms
QTcB	320	450	ms
RR	600	1200	ms

Spirometry

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

10.5. Appendix 5: Abbreviations

ADA	Anti-Palivizumab Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALRI	Acute Lower Respiratory Infection
ALT	Alanine Aminotransferase
AP	Analytical Plan
APTT	Activated Partial Thromboplastin Time
AR	Adverse Reaction
AST	Aspartate Aminotransferase
AST	Aspartate Transaminase
ATS	American Thoracic Society
AUC	Area Under the Curve
BD	Twice Daily
BMI	Body Mass Index
cGMP	Current Good Manufacturing Practices
CK	Creatine Kinase
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRP	C-reactive Protein
CYP450	Cytochrome 450
DNA	Deoxyribonucleic acid
DMID	Division of Microbiology and Infectious Disease
ECG	Electrocardiogram
ECSC	European Coal and Steel Community (
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
ERS	European Respiratory Society
EU	European Union
FEV	Forced Expiratory Volume
FOT	Forced oscillation technique
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HAV	Hepatitis A
HbA1c	Haemoglobin A1c
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
HVC	Human Viral Challenge
ICF	Inform Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committees
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IM	Intramuscular
IMP	Investigational Medicinal Product

IRB	Institutional Review Boards
IUD	Intrauterine Device
IV	Intravenous
LMIC	Low to Medium Income Country
LRT	Lower Respiratory Tract
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCID	Minimal Clinically Important Difference
MCV	Mean Corpuscular Volume
MHRA	Medicines and Healthcare products Regulatory Agency
MOI	Monoamine Oxidase Inhibitors
NIMP	Non-Investigational Medicinal Product
NPS	Nasopharyngeal Swab
PBMC	Peripheral Blood Mononuclear Cell
PCA	Principal Component Analysis
PCR	Polymerase Chain Reaction
PEF	Peak expiratory flow
PFM	Peak flow meter
PFU	Plaque Forming Unit
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PK	Pharmacokinetic
PT	Prothrombin Time
qRT-PCR	Quantitative Reverse Transcriptase-Polymerase Chain Reaction
RBC	Red Blood Cell
REC	Research Ethics Committee
RNA	Ribonucleic acid
RSI	Reference Safety Information
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SME	Sponsor's Medical Expert
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Adverse Reaction
T	Troponin
TDS	Three Times Daily
TMF	Trial Master File
TSH	Thyroid Stimulating Hormone
TSH	Thyroid Stimulating Hormone
TSS	Total Symptoms Score
UK	United Kingdom
URT	Upper Respiratory Tract
WBC	White Blood Cell
WHO	Word Health Organisation
β-HCG	β-human chorionic gonadotrophin

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