CLINICAL STUDY PROTOCOL

A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Immunogenicity and Efficacy of A Respiratory Syncytial Virus Vaccine (RSVpreF) in A Virus Challenge Model in Healthy Adults

Short Title:	Phase 2a Study of RSVpreF Vaccination and RSV Challenge in Healthy Adults
Version and Date of Protocol:	Final v3.0 _ Date 22 Jan 2021
Protocol Number:	HVO-CS-005
Sponsor:	[redacted]
Compound Number:	RSVpreF (PF-06928316)
EudraCT Number:	2020-003887-21

[redacted]

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]

Date

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 Signatory:

Name (typed or printed): [redacted]

Institution and Address: [redacted]

Signature: _____ Date: _____

(DD MMM YYYY)

[redacted]

Study Personnel Contact Information

CONTACT	DETAILS
Sponsor	[redacted]
Sponsor's Representative	[redacted]
Funder:	[redacted]
Principal Investigator (PI) and Clinical Trial Unit	[redacted]
Sponsor's Medical Monitor	Refer to the local study contact list document
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)	14 Sep 2020	Not applicable. First Version.
Amendment 01 (v2.0)	26 Oct 2020	Substantial Amendment
Amendment 02 (v3.0)	22 Jan 2021	Non-substantial Amendment

Amendment 01 (26-Oct-2020)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria	Update to exclusion criterion 4 to amend the upper limit of the body mass index to 30 kg/m2. Update to exclusion criterion 6 to include hypersensitivity to any component of the study vaccine. Clarification of exclusion criterion 9 related to the receipt of, or planning to receive, licensed vaccines before or after study vaccination and the viral challenge.	Protocol amendment in response to Grounds for Non-Acceptance and Request to Amend from the MHRA.
Section 6.5 Concomitant Therapies	Update to Table 3 (Permitted Medication) to remove the use of anti-depressants. The use of concomitant vaccination during an outbreak or a pandemic has been removed from exclusion criterion 9 and included into Section 6.5.	
Section 7.5 Stopping Rules	Amendment to correct inconsistencies, errors and duplications related to the study stopping rules. Stopping rule scenario related to SUSAR reporting in one (or more) participant(s) removed. The report of a SUSAR is covered by the reporting of SAR in one participant. Update added to all stopping rules to clarify that regulatory authority approval via a substantial amendment would be required in order to recommence the study.	

Amendment 02 (22-Jan-2021)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Section 7.2 Participant Discontinuation	Clarification that reserve vaccinated participants may not be inoculated with the challenge virus when the target evaluable number is achieved for a given quarantine group and for the overall study.	Minor clarification.

Table of Contents

List of Tables

1. Protocol Summary

1.1. Synopsis

Title	A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Immunogenicity and Efficacy of A Respiratory Syncytial Virus Vaccine (RSVpreF) in A Virus Challenge Model in Healthy Adults
Short Title	Phase 2a Study of RSVpreF Vaccination and RSV Challenged in Healthy Adults
Sponsor	[redacted]
Protocol number	HVO-CS-005
Eudract number	2020-003887-21
Phase	2a
Sites	Single centre, [redacted]
Indication	Prevention of RSV-associated moderate to severe lower respiratory tract disease in adults 60 years of age and older by active immunisation.
Study Type	Interventional
Design	Subjects will receive a single vaccination with either RSVpreF or Placebo one month prior to challenge with RSV-A Memphis 37b.
Investigational Medicinal Product (IMP)	PF-06928316 also known as RSVpreF
IMP dose(s)	120 mcg
Pharmaceutical form	Powder for solution for injection
IMP route(s)	Intramuscular
Control compound	Placebo
Randomisation	1:1
Challenge virus	RSV-A Memphis 37b
Challenge virus route	Intranasal delivery
Challenge virus titre	Total dose of approximately 4.5 $\log_{10}$ plaque forming units

Study population	Healthy male and female participants aged 18-50 years of age, screened for susceptibility to RSV infection, i.e., levels of RSV neutralizing antibodies compatible with susceptibility to RSV infection
Summary of study design	This is an exploratory proof-of-concept randomised, Phase 2a, double-blind, placebo-controlled study to evaluate the safety, immunogenicity and efficacy of an RSV vaccine against RSV-A Memphis 37b infection in healthy subjects. The study is divided into the following study phases: Screening: • Screening prior to vaccination from Day -84 to Day -29 (Day -118 for RSV serology). Pre-screening data collected through the hVIVO generic screening process prior to signing the study specific consent form, and prior to vaccination from Day -84 to Day -29 (Day -118 for RSV serology), may be transferred to this study after study-specific consent form has been signed by the participant. Pre-screening data obtained prior to this window can be re-assessed any time prior to vaccination from Day -84 to Day -29. Vaccination & follow up visits: • Vaccination on Day -28 (±3 days), participants will be randomised 1:1 to receive RSVpreF or placebo • Follow up clinic visit 1 day post vaccination • Follow up clinic visit 7 days post vaccination (±1 day) Quarantine & virus challenge: • Admission to the Quarantine Unit on Day -2/-1; resident in the Quarantine Unit for approximately 15 days, from admission on Day -2 to planned discharge on Day +12. • Challenge with Challenge Virus on Day 0. • Discharge from quarantine planned on Day +12 Follow-Up Clinic visits: • Day +28 (±3 days). • Day +155 (±14 days)
Expected duration of subject participation	Approximately 6 months from randomisation to the subject's last scheduled visit.
Overall duration of clinical phase	The length of the clinical phase is expected to be 9 months from start of vaccination for the first participant (FPFV) to the last scheduled study visit for the last participant (LPLV).
End of study	The end of the study will be considered as the last visit of the last participant in the study.

Procedures and assessments	During the study the following assessments and procedures will be performed:
	• Vaccination
	• Vaccination diary cards
	• Informed Consent
	• Medical History and Prior Medication Review (including hVIVO Medical Questionnaire)
	• Demographics
	• Height, Weight and Body Mass Index (BMI)
	• Complete Physical Examination
	• Directed Physical Examination
	• Vital Signs
	• Temperature
	• Electrocardiogram (ECG)
	• Spirometry
	• Subject Diary Cards
	  ○ Categorical Scale
	  ○ Visual Analogue Scale
	• Patient Health Questionnaire (PHQ-9)
	• Generalised Anxiety Disorder Questionnaire (GAD-7)
	• Nasal Discharge Collection
	• Blood Samples
	• Nasal Samples
	• Urine Collection
	• Breath Alcohol
	• AEs and Concomitant Medications

Sample size	Approximately 62 (up to 72) participants will be vaccinated. This will take account for withdrawals between vaccination and challenge.
Replacement policy	If a participant discontinues from study intervention OR withdraws from the study a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention as the participant being replaced. The replacement participant will be assigned a unique treatment/randomisation number.
Statistics	The statistical powering selected for this study is estimated to be sufficient for the primary objective and the primary endpoint family. The primary endpoint family consists of 3 endpoints listed below with their associated sample size estimates. As an exploratory proof of concept study, no adjustment for Type 1 error is planned in regard to the primary endpoint family. The sample size of 62 participants (31 in each arm) will allow: • Detection of a 70% relative reduction in the RT-PCR-AUC virology with RSVpreF assuming a 96% Coefficient of Variation (CV) in the control arm. The power for this endpoint is for 80% using a two-sided type-I error rate of 5%. The RT-PCR-AUC data is based on log transformed PCR data.

	• Detection of a 60% relative reduction in the symptomatic-infection rate with RSVpreF assuming a 59.26% rate in the control arm (i.e. a rate of 23.7% in the RSVpreF arm). The power for this endpoint is 80% using a two-sided type-I error rate of 5%. Symptomatic-infection is defined as: ○ Lab confirmed infection (two detectable (≥ Lower Limit of Detection LLOD) RT-PCR measurements (reported on 2 or more consecutive days), starting two days post-viral challenge (Day +2) up to discharge from quarantine), and ○ Either one or more positive clinical symptoms of any grade from two different categories in the symptom scoring system (Upper Respiratory, Lower Respiratory, Systemic), or one Grade 2 symptom from any category. • Detection of a 80% relative reduction in the sum total symptoms (sum of all symptom diary cards total score from day +1 post inoculation up to and including Day +12am) with RSVpreF assuming a 113.55% CV in the control arm. The power for this endpoint is at least 80% using a one-sided type-I error rate of 5%. The sample sizes indicate the number of vaccinated participants to be inoculated with the challenge virus per group, more will be vaccinated in order to achieve the inoculation numbers. Therefore, up to 72 participants will be enrolled and vaccinated with the study vaccine, with 62 participants challenged with the study virus.
OBJECTIVES	**ENDPOINTS**
PRIMARY	

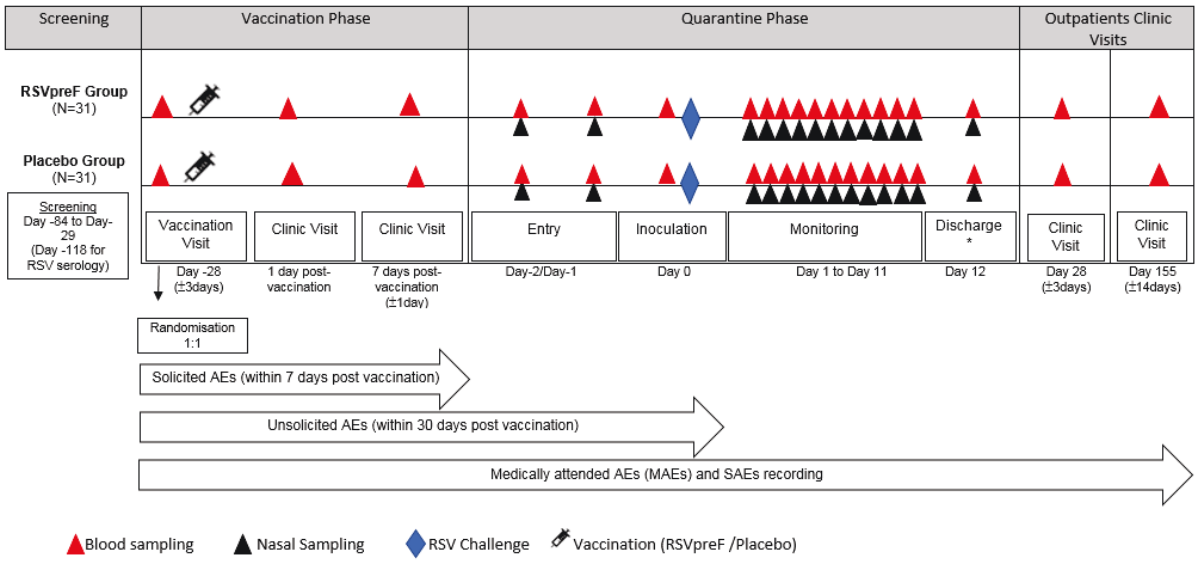
• To evaluate the effect of RSVpreF, in reducing the incidence or severity of infection or disease due to RSV-A Memphis 37b when compared to placebo	To evaluate the reduction in one or more of the following endpoints within the primary endpoint family: • Area under the viral load-time curve (VL-AUC) 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 discharge from quarantine. • RT-PCR-confirmed symptomatic RSV infection (Variant 1), defined as: ○ RT-PCR-confirmed RSV infection [two detectable (≥LLOD) qRT-PCR measurements (reported on 2 or more consecutive days), starting two days post-viral challenge (Day +2) up to discharge from quarantine], AND ○ Either one or more positive clinical symptoms of any grade from two different categories in the symptom scoring system (Upper Respiratory, Lower Respiratory, Systemic), or one Grade 2 symptom from any category • Sum total symptoms diary card score: sum total clinical symptoms (TSS) as measured by graded symptom scoring system collected three times daily starting one day post-viral challenge (Day +1) up to discharge from quarantine
SECONDARY	
• To further evaluate the effect of RSVpreF, in reducing the incidence of infection or disease due to RSV-A Memphis 37b, compared to placebo	To evaluate the reduction in the following endpoints: • RT-PCR-confirmed symptomatic RSV infection defined as: ○ RT-PCR-confirmed RSV infection (two quantifiable [≥LLOQ] qRT-PCR measurements (reported on 2 or more consecutive days), starting two days post-viral challenge [Day +2] up to discharge from quarantine.), AND ○ Either one or more positive clinical symptoms of any grade from two different categories in the symptom scoring system (Upper Respiratory, Lower Respiratory, Systemic), or one Grade 2 symptom from any category • Culture lab-confirmed reduction of symptomatic RSV infection defined as: ○ Lab-confirmed culturable RSV infection (one quantifiable (≥LLOQ) viral culture measurement starting two days post-viral challenge (Day +2) up to discharge from quarantine), AND ○ Either one or more positive clinical symptoms of any grade from two different categories in the symptom scoring system (Upper Respiratory, Lower Respiratory, Systemic), or one Grade 2 symptom from any category
• To further evaluate the effect of RSVpreF, in reducing infection due	To evaluate the reduction in the following endpoints: • Peak viral load of RSV-A Memphis 37b as defined by the maximum viral load determined by quantifiable qRT-PCR measurements in nasal samples

to RSV-A Memphis 37b compared to placebo	starting two days post-viral challenge (Day +2) up to discharge from quarantine. • Peak viral load of RSV-A Memphis 37b as defined by the maximum viral load determined by quantitative viral culture measurements in nasal samples starting two days post-viral challenge (Day +2) up to discharge from quarantine. • Duration of RSV-A Memphis 37b quantifiable qRT-PCR measurements in nasal samples starting two days post-viral challenge (Day +2) up to discharge from quarantine. Duration is defined as the time (hours) from first detectable until first confirmed undetectable assessment after their peak measure (after which no further virus is detected). • Duration of RSV-A Memphis 37b quantitative RSV viral culture measurements in nasal samples starting two days post-viral challenge (Day +2) up to discharge from quarantine. Duration is defined as the time (hours) from first detectable until first confirmed undetectable assessment after their peak measure (after which no further virus is detected). • Area under the viral load-time curve (VL-AUC) of RSV-A Memphis 37b as determined by quantitative viral culture on nasal samples starting two days post-viral challenge (Day +2) up to discharge from quarantine
• To further evaluate the effect of RSVpreF, in reducing symptomatic infection due to RSV-A Memphis 37b, compared to placebo	To evaluate the reduction in the following endpoints: • Area under the curve over time (TSS-AUC) of total clinical symptoms (TSS) as measured by graded symptom scoring system (categorical and visual analogue scales) collected three times daily starting one day post-viral challenge (Day +1) up to discharge from quarantine. • Peak symptoms diary card score: peak total clinical symptoms (TSS) as measured by graded symptom scoring system (categorical and visual analogue scales) collected three times daily starting one day post-viral challenge (Day +1) up to discharge from quarantine • Peak daily symptom score: Individual maximum daily sum of Symptom score starting one day post-viral challenge (Day +1) up to the end of quarantine. • Number (%) of participants with Grade 2 or higher symptoms
• To evaluate the effect of RSVpreF, in reducing the incidence of RSV-A Memphis 37b infection compared to placebo	To evaluate the reduction in the following endpoints: • Occurrence of at least two positive quantifiable (≥LLOQ) qRT-PCR measurements in nasal samples at different timepoints reported on 2 or more consecutive days starting two days post-viral challenge (Day +2) up to discharge from quarantine. • Occurrence of at least two positive detectable (≥LLOD) qRT-PCR measurements in nasal samples at different timepoints reported on 2 or more consecutive days starting two days post-viral challenge (Day +2) up to discharge from quarantine.

	• Occurrence of at least one positive quantitative (≥LLOQ) cell culture measurement in nasal samples starting two days post-viral challenge (Day +2) up to discharge from quarantine.
• To evaluate the effect of RSVpreF, in reducing nasal discharge, when compared to placebo	To evaluate the reduction in the following endpoints: • Total weight of mucus produced starting one day post-viral challenge (Day +1) up to discharge from quarantine. • Total number of tissues used by participants starting one day post-viral challenge (Day +1) up to discharge from quarantine.
• To evaluate the safety and reactogenicity of RSVpreF, when compared to placebo	To evaluate the incidence of the following endpoints: • Occurrence of solicited local reactions and systemic events within 7 days (i.e., on the day of vaccination and 6 subsequent days) after vaccination. • Occurrence of unsolicited adverse events (AEs) within 30 days (i.e., on the day of vaccination and 29 subsequent days) after vaccination • Occurrence of medically attended AEs (MAEs) and serious adverse events (SAEs) from vaccination (Day -28) up to study end (Day +155).
• To evaluate the safety of the RSV challenge model.	To list the incidence of the following endpoints: ○ Occurrence of unsolicited AEs within 30 days post-viral challenge (Day 0) up to Day +28 follow up. ○ Occurrence of SAEs related to the viral challenge from the viral challenge (Day 0) up to Day +28 follow up. ○ Occurrence of haematological and biochemical laboratory abnormalities during the quarantine period. • Use of concomitant medications within 30 days post-viral challenge (Day 0 up to Day +28 follow up).
TERTIARY Tertiary/exploratory endpoints include, but are not limited to the following.	
• To evaluate the effect of baseline immune status on immunogenicity and efficacy of the RSVpreF, when compared to placebo	• The primary, secondary, and tertiary endpoints may be explored in relation to the baseline status of participants and the response to vaccination.
• To characterize the innate, humoral and cellular immunity at a) baseline (prior to RSVpreF administration), b) after	The primary, secondary, and tertiary endpoints may be explored in relation to immunological levels at baseline, after vaccination, and after RSV challenge. Assays performed on serum and nasal samples may include, but are not limited to:

RSVpreF administration, and c) after RSV-A Memphis 37b challenge	• Humoral immunity / systems serology (for example RSV A & B neutralizing titres, PreF and PostF ELISAs to IgG, IgA, sIgA, ADCC) • Immunological measures of RSV A & B exposure/infection in community post vaccination • Proteomic levels and changes (for example, cytokine and chemokines) • Cellular cell quantification and quality of immunity (for example T and B cell frequencies, phenotypes and functionality assays: ELISPOTs, ICS, cytokine/chemokine responses) • Transcriptome levels and changes (for example, RNAseq, single cell RNAseq, microarray, PCR) • Genomics in relation to RSV susceptibility, infection and vaccine responsiveness (e.g. HLA typing, SNPs, GWAS)
• To evaluate the effect of RSVpreF, in reducing the incidence of RSV-A Memphis 37b disease, when compared to placebo	To evaluate the reduction in the incidence of: • Upper Respiratory Tract illness (URT) • Lower Respiratory Tract illness (LRT) • Systemic illness (SI) • Febrile illness (FI) • Proportion of Participants with Grade 2 or higher symptoms on any occasion at any time from the last assessment on Day 0 to quarantine discharge • Proportion of participants with Grade 2 or higher Symptoms on two separate occasions at any time from the last assessment on Day 0 to quarantine discharge • Proportion of participants with any symptom (grade >=1) on any occasion at any time from the last assessment on Day 0 to quarantine discharge • Proportion of participants with any symptom (grade >=1) on two separate occasions at any time from the last assessment on Day 0 to quarantine discharge

1.2. Study Schematic: On-study Participant Progression



*NOTE: Release from quarantine is foreseen at Day 12 in case no virus is detected by the nasal RSV discharge test 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. Schedule(s) of Activities (SoA)

Study Phase	Screening *	Visit 1	Visit 2	Visit 3	Visit 4																	Visit 5	Visit 6	Early Withdrawal	
		Outpatient			Inpatient Quarantine																	Follow-Up			
Study Day (with respect to challenge virus inoculation)	Day -84 to Day -29 (Day-118 for RSV serology)	Vaccination D -28 (+/-3days)	Clinic Visit 1 day post-vaccination	Clinic Visit 7 days post-vaccination (+/-1day)	D-2 (#)	D-1 (#)	Day 0 Pre	D0 Challenge	Day 0 Post	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D28 (+/- 3 days)	D155 (+/- 14 days)	Pre-Challenge	Post-Challenge
Written consent (a)	X	X																							
Eligibility criteria (+)	X	X			X[i]		X																		
Medical & medication history	X	X																							
Demographics	X																								
Height & weight, BMI (b)	X	X			X[i]																(X)	(X)	(X)	(X)	(X)
Patient Health Questionnaire (PHQ-9)	(X)	(X)			(X)[i]																				
Generalised Anxiety Disorder Questionnaire (GAD-7)	(X)	(X)			(X)[i]																				
Alcohol breath test	X	X			X[i]																	X	X		
Urinalysis	X	X		X	X[i]								X			X					X	X	X	X	X
Urine drugs of abuse and nicotine screen	X	X			X[i]																	X	X		
Urine pregnancy test	X	X																			X	X	X	X	X

Study Phase	Screening *	Visit 1	Visit 2	Visit 3	Visit 4																		Visit 5	Visit 6	Early Withdrawal	
		Outpatient			Inpatient Quarantine																		Follow-Up			
Study Day (with respect to challenge virus inoculation)	Day -84 to Day -29 (Day-118 for RSV serology)	Vaccination D -28 (+/-3days)	Clinic Visit 1 day post-vaccination	Clinic Visit 7 days post-vaccination (+/-1day)	D-2 (#)	D-1 (#)	Day 0 Pre	D0 Challenge	Day 0 Post	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D28 (+/- 3 days)	D155 (+/- 14 days)	Pre-Challenge	Post-Challenge
Complete physical examination	X	X			X[j]								X			X					X	X	X	X	X
Directed physical examination (inc nasal)							X		X	X	X	X		X	X		X	X	X	X					
Vital signs (HR, RR, SBP, DBP, SpO_2 (d)	X	2 X[n]			X	TDS	TDS			TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	X	X	X	X	X
Temperature (d)	X	2 X[n]			X	TDS	TDS			TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	TDS	X	X	X	X	X
Symptom diary card					X	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)
Spirometry (d)	X				X[j]								X			X				X		X	X		X
12-lead ECG	X				X[j]								X			X				X		X			X
Product Administration																										
Randomisation		X																								
Pre-Vaccination symptoms		X																								
IMP/Placebo Dosing		X																								
Post vaccination observation (o)		X																								
Vaccine symptom diary card distribution		X																								
Vaccine symptom diary card review			X	X																						

Study Phase	Screening *	Visit 1	Visit 2	Visit 3	Visit 4																		Visit 5	Visit 6	Early Withdrawal	
		Outpatient			Inpatient Quarantine																		Follow-Up			
Study Day (with respect to challenge virus inoculation)	Day -84 to Day -29 (Day-118 for RSV serology)	Vaccination D -28 (+/-3days)	Clinic Visit 1 day post-vaccination	Clinic Visit 7 days post-vaccination (+/-1day)	D-2 (#)	D-1 (#)	Day 0 Pre	D0 Challenge	Day 0 Post	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D28 (+/- 3 days)	D155 (+/- 14 days)	Pre-Challenge	Post-Challenge
Challenge Virus inoculation								X																		
Collection of blood samples																										
Serum FSH- (post-menopausal women)	X																									
Serum β-HCG pregnancy test (all females)		(X)[m]			X[i]																					
HIV, Hepatitis A, B, & C	X																									
Haematology (e)	X				X[i]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry	X	(X)			X[i]								X			X				X		X	X	X	X
Coagulation	X	(X)			(X)[i]																					
Cardiac enzymes	X				X[i]								X			X				X					
Thyroid function test	X				(X)[i]																					
Blood - serum markers Humoral immunity (f) (g)	X	X			X[i]																X	X	X	X	X	X
Blood – serum markers cytokines/chemokines (g)		X	X		X[p]					(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)					
Blood - PBMCs CMI & cellular markers (g)		X		X	X[p]														X			X	X	(X)	(X)
Blood Paxgene, (DNA – Genomics)		X [r]																								

Study Phase	Screening *	Visit 1	Visit 2	Visit 3	Visit 4																	Visit 5	Visit 6	Early Withdrawal	
		Outpatient			Inpatient Quarantine																	Follow-Up			
Study Day (with respect to challenge virus inoculation)	Day -84 to Day -29 (Day-118 for RSV serology)	Vaccination D -28 (+/-3days)	Clinic Visit 1 day post-vaccination	Clinic Visit 7 days post-vaccination (+/-1day)	D-2 (#)	D-1 (#)	Day 0 Pre	D0 Challenge	Day 0 Post	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D28 (+/- 3 days)	D155 (+/- 14 days)	Pre-Challenge	Post-Challenge
Blood Paxgene (Transcriptomics)		X	X		X[p]					(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)				
Collection of respiratory samples																									
Nasal sample - Respiratory pathogen screen (h)	T	X			X	(X)																			
Nasal sample - RSV discharge test																				(X)[q]	(X)[q]				
Nasosorption – Ig, Cytokine and chemokine quantification		(X)	(X)		(X)[p]					(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)				
Nasal sample – Virology (i)	T					X					BD	BD	BD	BD	BD	BD	BD	BD	BD	BD	X				
Safety Assessments																									
Solicited AE recording (k)	X	←	→																						
Unsolicited AE recording (l)		←	→																						
Medically Attended AEs (MAEs) and SAE recording		←	→																						
Concomitant medications	X	←	→																						

KEY NOTES FOR 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).
*	All screening assessments will be performed under hVIVO Generic Screening process. Results of tests or examinations performed under hVIVO Generic Screening process, and from Day -118 (Day -118 for viral serology and Day-84 for other assessments including safety laboratory test) prior to vaccination may be used to determine eligibility without the need to repeat the assessment following study specific consent.
+	Only the applicable Inclusion/Exclusion criteria will be reviewed at each time point.
#	Admission can occur on Day -2 or Day -1 and therefore procedures can be performed on Day-2 or Day-1. If admission is on Day -1 then those procedures which occur on both Day -2 and -1 will only be captured using the timepoints of Day -1. For TDS assessments on Day -2/Day-1: When Quarantine Admission occurs on Day -1, assessments will be performed up to three times daily.
a	Study-specific consent may occur on the day of vaccination, providing all required eligibility information has been collected through the hVIVO generic screening process.
b	Height will be taken at Screening only.
c	Distribution of paper tissues and bags will start on Day -1, with the first collection on Day 0. Thereafter collection of tissues will occur at the same timepoints (± 1 hour) with tissues distributed 24h ahead.
d	Assessments will be performed at the same time each day during quarantine (± 1 hour).
e	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).
f	Vaccine and viral challenge serology (e.g. RSV neutralisation antibody assay) will be performed to determine eligibility and seroconversion. Non-vaccine antigen-binding antibody assay will be used for serological detection/seroconversion of community acquired RSV infection between vaccination and viral challenge.
g	Samples for related exploratory research.

h	Upper respiratory tract swab (e.g. nasopharyngeal swab, mid-turbinate swab, oropharyngeal swab) for respiratory virus screen to assess for the presence of other respiratory viruses; if found positive for any pathogen in the panel, the participant will not be eligible for the current quarantine. Sample will also be tested for SARSCoV-2 (COVID-19), which would contraindicate the participant's participation.
i	Pre-inoculation nasal samples are optional under PI discretion. Post inoculation Nasal virology samples will be collected at the same time each day during quarantine (± 1 hour) and used for RT-qPCR and viral culture assay (as appropriate). Samples may be used for related exploratory research.
j	Can be performed on Study Day -2 or Study Day -1.
k	Solicited reactogenicity will be collected from vaccination until 7 days after vaccination.
l	Unsolicited AEs will be collected from vaccination until 30 days after vaccination.
m	Blood serum pregnancy test (ß-HCG) will be performed in all female participants who have been tested positive for urine pregnancy testing.
n	Assessments to be made pre and post dosing.
o	Participants will be closely observed for a minimum of 30 minutes post-vaccination. Any unsolicited, solicited AEs, and vital signs will be documented by the Investigator following this observation period.
p	Sample will be taken on Day -2, Day-1 or Day 0 pre-challenge.
q	Nasal sample for RSV discharge test will be collected on Day 11 or Day 12. A repeat test may be requested at PI discretion at subsequent days.
r	Sample collected only for subjects who consented to genetic testing. If a Day -28 sample is not taken, then it may be taken on the clinic visit 1 day post vaccination instead.
Notes:	Parenthesis indicates the assessment may be optional (will be identified in the Research Plan), or at the PI's discretion. The PI may perform additional safety assessments as required. For all participants TDS assessments will commence on Day 0, the first assessment will be pre-virus challenge. Where any nasal sampling time points occur together, the order of sampling will typically be (1) Nasosorption followed by (2) Nasopharyngeal swab followed by (3) Nasal wash.

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

2. Introduction

RSVpreF is being developed to prevent RSV-associated moderate to severe lower respiratory tract disease in adults 60 years of age and older by active immunisation (older adult indication) and to prevent RSV-associated LRTI in infants by active immunisation of pregnant women (maternal indication).

This study will be an exploratory proof of concept Phase 2a study for the older adult indication assessing the RSVpreF vaccine immunogenicity and efficacy in the RSV-A Memphis 37b human challenge model.

- VACCINE

  The aim of RSV immunisation in adults 60 years of age and over is to boost the immune response sufficiently to protect against RSV disease. There are 2 antigenic variants of RSV, namely, RSV subgroup A (RSV A) and RSV subgroup B (RSV B). The RSV vaccine (RSVpreF) being investigated in this study is bivalent, composed of two stabilised RSV prefusion F antigens, each representing one subgroup, to optimise the breadth of protection against all circulating strains. RSV F facilitates fusion of the virion and host cell membrane during cell entry through a dramatic transition from metastable prefusion confirmation to a very stable postfusion state. Preclinical studies show that prefusion F, when engineered to maintain the prefusion conformation, elicits much higher neutralising antibody titres than postfusion F and that the most potent neutralising antibodies from post-infection human sera target the prefusion form,

- PRECLINICAL AND CLINICAL STUDIES.

  Pfizer's RSVpreF has been evaluated in preclinical studies demonstrating robust RSV A– and RSV B–neutralising antibody responses in mice, cotton rats, and nonhuman primates. RSVpreF, with or without aluminum hydroxide (Al[OH]3), is currently being evaluated in a Phase 1/2, placebo controlled, randomised, observer-blind, dose-finding, first-in-human (FIH) study in healthy adults 18 to 85 years old (C3671001). This study is also assessing RSVpreF vaccination with and without concomitant influenza vaccination. In an ongoing Phase 1/2, placebo-controlled randomised, observer-blind, dose-ranging, FIH study (C3671002), a CpG adjuvant containing formulation is being evaluated in older adults 65 to 85 years of age. RSVpreF has demonstrated an acceptable safety profile in these studies. Interim immunogenicity data demonstrated high neutralising antibody responses to the stabilized prefusion F antigens in RSVpreF. The maternal indication is supported by a Phase 2b, placebo-controlled, randomised, observer-blind study in healthy pregnant women 18 to 49 years of age assessing RSVpreF with and without $Al(OH)_3$ (C3671003) and a Phase 2b, placebo-controlled, randomised, observer-blind study investigating concomitant administration of RSVpreF and a tetanus, diphtheria, acellular pertussis vaccine (Tdap) in healthy nonpregnant women 18 to 49 years of age (C3671004). A Phase 3, placebo-controlled, randomised, double-blind study has recently started to evaluate efficacy and safety of RSVpreF in infants born to women vaccinated during pregnancy (C3671008). There are no safety concerns at this time. Comprehensive non-clinical and clinical information regarding RSVpreF is further described in the Investigator's Brochure (IB).

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).

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). RSV is a predictable seasonal cause of respiratory illness that burdens the healthcare system, resulting in increased numbers of medical visits, hospitalizations, and deaths. Published estimates indicate that approximately 11,000 to 17,000 older adults die annually of RSV-related illnesses in the United States (US), with about 10-fold more (177,500) admitted to the hospital with respiratory symptoms (Matias et al. 2014; Walsh and Falsey 2012). Adults with underlying risk factors may present with RSV-associated disease of increased severity and duration. RSV may also trigger clinical deterioration in frail older adults, the immunocompromised, and those with chronic cardio-pulmonary disease, resulting in RSV-associated hospitalization (Falsey et al. 2005; Zhou et al. 2012; Fleming et al. 2015). No vaccine to treat or prevent RSV mediated disease is currrently available.

The RSV human challenge model was developed to not only aid understanding of RSV disease, but also to 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 1300 healthy participants (18 to 55 years of age) and has 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 in heathy adults is characterised by an abrupt onset of rhinitis, nasal stuffiness, sore throat, cough, malaise, and myalgia (muscle aches). In healthy adults, the illness usually resolves without any treatment, with relief of symptoms occurring naturally within 7 to 10 days.

RSV Vaccines

Despite the significant medical need, there are currently no vaccines approved for the prevention of lower respiratory tract illness caused by RSV and treatment options are limited. The first vaccine candidate for RSV naïve young children, which consisted of formalin-inactivated RSV (FI-RSV), was associated with enhanced respiratory disease (ERD) upon infection with RSV (Kapikian et al. 1969). Although the mechanisms for ERD are not fully understood, it is thought that FI-RSV failed to induce adequate

neutralizing antibody titers and CD8 priming and induced a T-helper (Th) 2 skewed response (Moghaddam et al. 2006).

An investigational adenovirus vectored virus RSV vaccine with the pre-fusion F protein (Ad26.RSV.preF) has recently progressed through the human RSV-A Memphis 37b challenge model (NCT03334695). There were no safety concerns reported and exploratory endpoint efficacy was shown by significant reduction in viral replication (DeVincenzo et al. 2019).

RSVpreF

The RSV F protein undergoes a conformational transition from a metastable pre-fusion state to a stable post-fusion conformation. Neutralizing sensitive epitopes specific to the pre-F protein are more potent than those that only bind post-F protein (Gilman et al. 2016; Graham, Modjarrad, and McLellan 2015). The creation of a stabilised prefusion F confirmation that is highly immunogenic and induces robust neutralisation antibodies forms the basis of the RSVpreF evaluated in this protocol.

An efficacious RSV vaccine is expected to induce high levels of neutralising antibodies. RSVpreF under evaluation in this protocol has been shown to promote a strong antibody response.

2.1. Study Rationale

This is an exploratory proof of concept randomised, Phase 2a, double-blind, placebo-controlled human challenge study in healthy adults. Participants will receive a single intramuscular dose of either RSVpreF or placebo and 4 weeks later undergo intranasal challenge with RSV-A Memphis 37b virus. The immunogenicity and efficacy of RSVpreF vaccination on virus replication, clinical symptoms, and incidence of symptomatic RSV infection compared to placebo will be evaluated.

This study will serve as a pilot to explore the efficacy of RSVpreF in the human challenge model. Despite the exploratory descriptive nature of the study, a primary objective is included. To explore the primary objective, significant reductions in any one of the three primary endpoints (primary endpoint family) will be explored. The primary endpoint family includes both an objective for a virological endpoint (reduction of area under curve of viral load,VL-AUC) and two subjective clinical based endpoints (reduction in sum total symptom score and incidence of symptomatic infection). Additional key secondary endpoints are included relating to reductions in clinical symptoms (AUC, peak and duration), reduction in mucous secretions, as well as several definitions of incidence of infection and symptomatic infection that include varying degrees of severity of symptoms within their definitions. Furthermore, the baseline immunity of the participants prior to vaccination will be explored in relation to RSVpreF responsiveness, and RSVpreF induced immune responses will be correlated with protection from RSV-A Memphis 37b infection and disease.

2.2. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected Adverse Events (AEs) of RSVpreF may be found in the IB.

2.2.1. Risk Assessment

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

During a pandemic, additional potential risks to participants may include interruptions to study visit schedule, adherence to protocol-specified safety monitoring or safety laboratory assessments. Refer to COVID-19 Crisis Management Plan for further details on the risks and risk mitigation strategy.

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
Study Intervention		
Intramuscular Dosing with RSVpreF	Prior studies showed RSVpreF to have an acceptable safety profile as described in Section 2. Signs and symptoms observed after vaccination with RSVpreF include fatigue/tiredness, muscle pain, headache, and joint pain. These were mild or moderate.	These potential reactions, if they are observed, will be monitored but are generally short-term and do not require treatment.
	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.
	Systemic exposure to RSVpreF	To minimise any risks associated with systemic exposure to RSVpreF, male and female participants must be on highly effective contraception methods during the study as described is Section 5.1.
General Risks related to Vaccines	General signs and symptoms associated with administration of a vaccine, or vaccination with placebo, including fatigue, headache, myalgia, arthralgia, chills and nausea.	These side effects will be monitored but are generally short-term and do not require treatment.
	An allergic reaction to the vaccination. may cause a rash, hives or even difficulty breathing. Severe reactions, including anaphylaxis, are rare but can occur with any vaccine.	Medications 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 to vaccines or vaccine components will be excluded from the study. The study site should have medical treatment available in case of severe allergic reactions following vaccine administration.

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
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 a viral diagnostic (e.g. RVAT, PCR) to determine participants' suitability for departure.
	Passing the RSV Challenge Virus to others, including vulnerable people (see below for definition of vulnerable populations).	Participants will remain in individual isolated rooms in the quarantine unit for 12 days after inoculation with the challenge virus.

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
		To reduce the risk of transmitting the virus into the community, participants will be asked to avoid, where possible, contact with vulnerable people for 14 days after they leave quarantine (Section 2.2.1.1).
	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 IB for detailed information.		

2.2.1.1. 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)

2.2.2. Benefit Assessment

Healthy participants who receive the study vaccine may not directly benefit from this vaccination as the efficacy of the vaccine has not yet been demonstrated.

Participants may develop some immunity to RSV 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 vaccines in an area of unmet medical need.

2.2.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants in this study, the potential risks identified in association with RSVpreF are justified by the anticipated benefits linked to the evaluation of RSVpreF in the viral challenge model which will subsequently facilitate future assessment of RSV vaccines.

3. Objectives and Endpoints

OBJECTIVES	ENDPOINTS
PRIMARY	
• To evaluate the effect of RSVpreF, in reducing the incidence or severity of infection or disease due to RSV-A Memphis 37b when compared to placebo	To evaluate the reduction in one or more of the following endpoints within the primary endpoint family: • 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 discharge from quarantine. • RT-PCR-confirmed symptomatic RSV infection (Variant 1), defined as: o RT-PCR-confirmed RSV infection [two detectable (≥LLOD) qRT-PCR measurements (reported on 2 or more consecutive days), starting two days post-viral challenge (Day +2) up to discharge from quarantine], AND o Either one or more positive clinical symptoms of any grade from two different categories in the symptom scoring system (Upper Respiratory, Lower Respiratory, Systemic), or one Grade 2 symptom from any category • Sum total symptoms diary card score: sum total clinical symptoms (TSS) as measured by graded symptom scoring system collected three times daily starting one day post-viral challenge (Day +1) up to discharge from quarantine
SECONDARY	

• To further evaluate the effect of RSVpreF, in reducing the incidence of infection or disease due to RSV-A Memphis 37b, compared to placebo	To evaluate the reduction in the following endpoints: • RT-PCR-confirmed symptomatic RSV infection defined as: o RT-PCR-confirmed RSV infection (two quantifiable [≥LLOQ] qRT-PCR measurements (reported on 2 or more consecutive days), starting two days post-viral challenge [Day +2] up to discharge from quarantine.), AND o Either one or more positive clinical symptoms of any grade from two different categories in the symptom scoring system (Upper Respiratory, Lower Respiratory, Systemic), or one Grade 2 symptom from any category • Culture lab-confirmed reduction of symptomatic RSV infection defined as: o Lab-confirmed culturable RSV infection (one quantifiable (≥LLOQ) viral culture measurement starting two days post-viral challenge (Day +2) up to discharge from quarantine), AND o Either one or more positive clinical symptoms of any grade from two different categories in the symptom scoring system (Upper Respiratory, Lower Respiratory, Systemic), or one Grade 2 symptom from any category
• To further evaluate the effect of RSVpreF, in reducing infection due to RSV-A Memphis 37b compared to placebo	To evaluate the reduction in the following endpoints: • 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 discharge from quarantine. • Peak viral load of RSV-A Memphis 37b as defined by the maximum viral load determined by quantitative viral culture measurements in nasal samples starting two days post-viral challenge (Day +2) up to discharge from quarantine. • Duration of RSV-A Memphis 37b quantifiable qRT-PCR measurements in nasal samples starting two days post-viral challenge (Day +2) up to discharge from quarantine. Duration is defined as the time (hours) from first detectable until first confirmed undetectable assessment after their peak measure (after which no further virus is detected). • Duration of RSV-A Memphis 37b quantitative RSV viral culture measurements in nasal samples starting two days post-viral challenge (Day +2) up to discharge from quarantine. Duration is defined as the time (hours) from first detectable until first confirmed undetectable assessment after their peak measure (after which no further virus is detected). • Area under the viral load-time curve (VL-AUC) of RSV-A Memphis 37b as determined by quantitative viral culture on nasal samples starting two days post-viral challenge (Day +2) up to discharge from quarantine

• To further evaluate the effect of RSVpreF, in reducing symptomatic infection due to RSV-A Memphis 37b, compared to placebo	To evaluate the reduction in the following endpoints: • Area under the curve over time (TSS-AUC) of total clinical symptoms (TSS) as measured by graded symptom scoring system (categorical and visual analogue scales) collected three times daily starting one day post-viral challenge (Day +1) up to discharge from quarantine. • Peak symptoms diary card score: peak total clinical symptoms (TSS) as measured by graded symptom scoring system (categorical and visual analogue scales) collected three times daily starting one day post-viral challenge (Day +1) up to discharge from quarantine • Peak daily symptom score: Individual maximum daily sum of Symptom score starting one day post-viral challenge (Day +1) up to the end of quarantine. • Number (%) of participants with Grade 2 or higher symptoms
• To evaluate the effect of RSVpreF, in reducing the incidence of RSV-A Memphis 37b infection compared to placebo	To evaluate the reduction in the following endpoints: • Occurrence of at least two positive quantifiable (≥LLOQ) qRT-PCR measurements in nasal samples at different timepoints reported on 2 or more consecutive days starting two days post-viral challenge (Day +2) up to discharge from quarantine. • Occurrence of at least two positive detectable (≥LLOD) qRT-PCR measurements in nasal samples at different timepoints reported on 2 or more consecutive days starting two days post-viral challenge (Day +2) up to discharge from quarantine. • Occurrence of at least one positive quantitative (≥LLOQ) cell culture measurement in nasal samples starting two days post-viral challenge (Day +2) up to discharge from quarantine.
• To evaluate the effect of RSVpreF, in reducing nasal discharge, when compared to placebo	To evaluate the reduction in the following endpoints: • Total weight of mucus produced starting one day post-viral challenge (Day +1) up to discharge from quarantine. • Total number of tissues used by participants starting one day post-viral challenge (Day +1) up to discharge from quarantine.
• To evaluate the safety and reactogenicity of RSVpreF, when compared to placebo	To evaluate the incidence of the following endpoints: • Occurrence of solicited local reactions and systemic events within 7 days (i.e., on the day of vaccination and 6 subsequent days) after vaccination. • Occurrence of unsolicited adverse events (AEs) within 30 days (i.e., on the day of vaccination and 29 subsequent days) after vaccination • Occurrence of medically attended AEs (MAEs) and serious adverse events (SAEs) from vaccination (Day -28) up to study end (Day +155).

• To evaluate the safety of the RSV challenge model.	To list the incidence of the following endpoints: o Occurrence of unsolicited AEs within 30 days post-viral challenge (Day 0) up to Day +28 follow up. o Occurrence of SAEs related to the viral challenge from the viral challenge (Day 0) up to Day +28 follow up. o Occurrence of haematological and biochemical laboratory abnormalities during the quarantine period. • Use of concomitant medications within 30 days post-viral challenge (Day 0 up to Day +28 follow up).
TERTIARY Tertiary/exploratory endpoints include but are not limited to the following.	
• To evaluate the effect of baseline immune status on immunogenicity and efficacy of the RSVpreF, when compared to placebo	• The primary, secondary, and tertiary endpoints may be explored in relation to the baseline status of participants and the response to vaccination.
• To characterize the innate, humoral and cellular immunity at a) baseline (prior to RSVpreF administration), b) after RSVpreF administration, and c) after RSV-A Memphis 37b challenge	The primary, secondary, and tertiary endpoints may be explored in relation to immunological levels at baseline, after vaccination, and after RSV challenge. Assays performed on serum and nasal samples may include, but are not limited to: • Humoral immunity / systems serology (for example RSV A & B neutralizing titres, PreF and PostF ELISAs to IgG, IgA, sIgA, ADCC) • Immunological measures of RSV A & B exposure/infection in community post vaccination • Proteomic levels and changes (for example, cytokine and chemokines) • Cellular cell quantification and quality of immunity (for example T and B cell frequencies, phenotypes and functionality assays: ELISPOTs, ICS, cytokine/chemokine responses) • Transcriptome levels and changes (for example, RNAseq, single cell RNAseq, microarray, PCR) • Genomics in relation to RSV susceptibility, infection and vaccine responsiveness (e.g. HLA typing, SNPs, GWAS)

• To evaluate the effect of RSVpreF, in reducing the incidence of RSV-A Memphis 37b disease, when compared to placebo	To evaluate the reduction in the incidence of: • Upper Respiratory Tract illness (URT) • Lower Respiratory Tract illness (LRT) • Systemic illness (SI) • Febrile illness (FI) • Proportion of Participants with Grade 2 or higher symptoms on any occasion at any time from the last assessment on Day 0 to quarantine discharge • Proportion of participants with Grade 2 or higher Symptoms on two separate occasions at any time from the last assessment on Day 0 to quarantine discharge • Proportion of participants with any symptom (grade >=1) on any occasion at any time from the last assessment on Day 0 to quarantine discharge • Proportion of participants with any symptom (grade >=1) on two separate occasions at any time from the last assessment on Day 0 to quarantine discharge

4. Study Design

4.1. Overall Design

This is a randomised, Phase 2a, double blind, placebo-controlled study to evaluate the safety, immunogenicity and efficacy of an RSV vaccine against RSV-A Memphis 37b infection in healthy participants.

The total duration of study participation for a participant is approximately 6 months after vaccination, with the following sequence and duration of study periods:

Screening Phase:

- Screening prior to vaccination from Day -84 to Day -29 (Day -118 for RSV serology) Pre-screening data collected through the hVIVO generic screening process prior to signing the study specific consent form, and prior to vaccination from Day -84 to Day -29Day -118 for days for RSV serology) may be transferred to this study after study-specific consent form has been signed by the participant. Pre-screening data obtained prior to this window can be re-assessed any time prior to vaccination from Day -84 to Day -29.

Vaccination Phase:

- Vaccination on Day -28 (±3 days), participants will be randomised 1:1 to receive RSVpreF or placebo
- Follow up clinic visit 1 day post vaccination
- Follow up clinic visit 7 days post vaccination (±1 day)

Quarantine Phase:

- Admission to the Quarantine Unit on Day -2/-1; resident in the Quarantine Unit for approximately 15 days, from admission on Day -2 to planned discharge on Day +12.
- Challenge with Challenge Virus on Day 0.
- Discharge from quarantine planned on Day +12

Follow-Up Phase:

- Day +28 (±3 days).
- Day +155 (±14 days)

Participants will be pre-screened for susceptibility to RSV infection, i.e., have levels of RSV neutralising antibodies compatible with susceptibility to RSV infection.

Participants will be randomised to receive a single intramuscular dose of RSVpreF or Placebo on Day -28 (±3 days):

- **Reference article product**
    - PF-06928316 also known as RSVpreF
    - Dose: 120mcg

- **Placebo product**
    - Placebo to match vaccine

All participants will be closely observed for a minimum of 30 minutes post-vaccination, to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited AEs and vital signs will be documented by study-site personnel following this observation period. Participants will be given a thermometer, a calliper/ruler and a vaccination diary card [VDC] (for daily assessment of symptoms) with instructions for the completion of the diary card. Each participant will record the presence/absence of symptoms, solicited AEs, and oral temperatures, beginning on the evening of the study vaccine dosing day (Day -28) and daily for a total of 7 days. Reminders (e.g. via text message will be sent to participants from study site personnel to ensure compliance with the VDC. A study site personnel will collect and review the participant completed vaccination diary card at the post-vaccination clinic visit, approximately 7 days post vaccination and review the information and confirm the entries. Participants will be provided with an Emergency Contact Card to contact the Investigator when potentially severe reaction occurs.

Post-vaccination clinic visits will occur 1 day post vaccination and approximately 7 days post-vaccination. Any unsolicited, solicited AEs and vital signs will be documented by the Investigator. Any clinically significant symptom/AE persisting after the 7 days will be followed up by the Investigator until resolution or until clinically stable outcome is reached.

One to two days prior to viral challenge, participants will be admitted to the quarantine unit. Quarantine assessments will include relevant information since vaccination, ECG, Spirometry, Physical Examination and clinical laboratory testing. Participants 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

Participants will reside in the Quarantine Unit for a total of approximately 15 days (from Day -2 to Day 12). From Day 2 to Day 11, nasal samples will be collected approximately every 12 hours, and physical examination, vital signs measurements, ECG, clinical safety laboratory test, and Spirometry will be performed as per the Schedule of Activities (SOA) in Section 1.3. Release from quarantine is foreseen at Day 12, provided no virus is detected (by either the qualitative virus antigen test (RVAT) or equivalent viral test, as appropriate) 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 based on the assessment of the Investigator. If appropriate, participants may reside in quarantine for an additional night or longer before discharge.

Participants will attend a follow up visit at 28 days post-challenge (Day 28), and a follow-up visit at 6 months post-vaccination.

4.2. Scientific Rationale for Study Design

The study will be conducted by hVIVO Services Limited, 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 1300 participants have been successfully and safely inoculated with RSV-A Memphis 37b strain. These studies demonstrated that adults could be infected by

nasal inoculation and that experimental infection was safe. This RSV-A Memphis 37b strain has been shown to cause symptoms and virus shedding that closely match natural infection in healthy adults.

Administration of study intervention and challenge with RSV-A Memphis 37b strain 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 nasal secretions for assessment of safety and efficacy) have been employed in previous studies conducted by hVIVO.

Further details of study rational are included in Section 2.1.

4.3. Justification for Dose

Three studies have compared different dose levels and formulations of RSVpreF.

- The first-in-human (FIH) study in adults 18 to 85 years of age evaluated the safety, tolerability, and immunogenicity of 3 escalating dose levels of 60 µg, 120 µg, and 240 µg, with or without $Al(OH)_3$, when administered alone or concomitantly with seasonal inactivated influenza vaccine (SIIV) (C3671001).
- A study in older adults 65 to 85 years of age evaluated safety, tolerability and immunogenicity of 60 µg, 120 µg, and 240 µg RSVpreF doses formulated with $Al(OH)_3$ or CpG/$Al(OH)_3$- adjuvant ,or 240 µg RSVpreF with RSV antigens alone , when administered concomitantly with SIIV (C3671002).
- A study in pregnant women 18 to 49 years of age evaluated safety tolerability and immunogenicity of 120 µg and 240 µg RSVpreF dose levels with and without $Al(OH)_3$ (C3671003).

In none of these studies were substantial differences between the immunogenicity or reactogenicity of 120 mg and 240 mg dose levels or of formulations with and without $Al(OH)_3$ observed. Therefore, 120 mg without $Al(OH)_3$ is chosen for the human challenge study.

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 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	[redacted] STANDARD INCLUSION CRITERIA
To be eligible for the study, participants must meet all the following inclusion criteria:	
1	An informed consent document signed and dated by the participant and the Investigator.
2	Aged between 18 and 50 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), 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 28 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:

NO	[redacted] STANDARD INCLUSION CRITERIA
To be eligible for the study, participants must meet all the following inclusion criteria:	
	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 28 days after the date of Viral challenge / last dosing with 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 28 days after the date of Viral Challenge/last dosing with IMP (whichever occurs last).
7	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	[redacted] STANDARD EXCLUSION CRITERIA
Participants who meet any of the following exclusion criteria will not be included in the study.	
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 (e.g autoimmune disease or immunodeficiency). ***Guidance*** *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).* • *Any rhinitis (specifically upper respiratory tract symptoms related to 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 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.*

NO	[redacted] STANDARD EXCLUSION CRITERIA
Participants who meet any of the following exclusion criteria will not be included in the study.	
	• *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 or vaccine, including hypersensitivity to any of the constituents of the study vaccine, as assessed by the PI.
7	Venous access deemed inadequate for the phlebotomy and cannulation demands of the study.
8	a) 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	a) Evidence of vaccinations with licensed live attenuated vaccines within the 4 weeks prior to the planned date of viral challenge/first dosing with IMP (whichever occurs first). Evidence of vaccinations with licensed vaccines which are not live attenuated within the 2 weeks prior to the planned date of viral challenge/first dosing with IMP (whichever occurs first). b) Intention to receive any vaccination(s) before at least 28 days after the viral challenge (NB. No travel restrictions will apply after the Day 28 Follow-up visit).
10	Receipt of blood or blood products, or loss (including blood donations) of 550 mL or more of blood during the 2 months prior to the planned date of viral challenge/first dosing with IMP (whichever occurs first) or planned during the 2 months after the viral challenge.
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	[redacted] STANDARD EXCLUSION CRITERIA
Participants who meet any of the following exclusion criteria will not be included in the study.	
	b) Previous vaccination with any licensed or investigational RSV vaccine before enrolment into the study. c) 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). d) Prior inoculation with a virus from the same virus-family as the challenge virus. e) 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. f) Receipt of treatment with immunosuppressive therapy.
12	a) Confirmed positive test for drugs of abuse and cotinine 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	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, Pfizer or any vendor.
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.

Participants must not consume any food containing poppy seeds or any codeine containing formulation starting 72 hours before screening, before vaccination and before admission to the quarantine Unit (in order to avoid false-positive urine drug screen).

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 or use tobacco or 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 must refrain 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) in order to avoid potential spurious elevation of clinical laboratory safety parameters.

5.4. Screen Failures

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

If an individual does not meet the criteria for participation in this study (screen failure) and the Investigator would like to re-screen the participant, and they are still within the allowed screening window (Day -118 to Day -29), then only the assessments for which the participant failed must be re-assessed.

If an individual does not meet the criteria for participation in this study (screen failure) and the Investigator would like to re-screen the participant at a later time (i.e. outside of the allowed screening window), then full re-screening must be completed.

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6. Study Intervention

Study interventions administered to participants are described in Table 1.

6.1. Study Intervention(s) Administered

Table 1 Study Interventions

Intervention Name	**RSVpreF**	**Placebo**	**RSV-A Memphis 37b virus]**
Type	Biologic	Other	Virus
Dose Formulation	The active ingredients in RSVpreF are 2 stabilized RSV prefusion F antigens, in equal amounts from virus subgroups A and B, in a lyophilized dosage form for reconstitution. The drug product is supplied as a lyophilized white cake in a 2-mL glass vial, with a 13-mm lyophilization stopper, aluminum overseal, and flip-off cap. The drug product will be reconstituted by a diluent consisting of sterile water in a prefilled syringe (PFS).	Placebo will be a lyophile match to the vaccine, which will consist of excipients matched to those used in the RSVpreF formulation, minus the active ingredients. The physical appearance of the reconstituted RSVpreF and placebo will be matched, and the study will be conducted in a double-blinded manner.	Cryovial, Liquid
Unit Dose Strength(s)	120mcg vial	0.5mL/vial	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 4.5$\log_{10}$ PFU.
Dosage Level(s)	A single unit dose of 120 mcg RSVpreF will be reconstituted with sterile water for an 0.5 mL injection volume	The fill volume of the placebo vial and diluent prefilled syringe is designed that the intended dose is delivered in a 0.5 mL injection volume.	A single dose of virus will be delivered. Dose volume delivery method is provided in the Analytical Plan (AP).
Route of Administration	Intramuscular injection in left arm	Intramuscular injection in left arm	Intranasal
Use	Experimental reference article	Placebo control	Infectious challenge agent

IMP and NIMP	IMP	IMP	NIMP challenge virus
Sourcing	[redacted]	[redacted]	[redacted]
Packaging and Labelling	The details of the study intervention packaging and labelling will be provided in the study-specific Pharmacy Manual.	The details of the study intervention packaging and labelling will be provided in the study-specific Pharmacy Manual.	RSV Challenge Inoculum will be provided in vials. The details of the virus challenge agent packaging and labelling will be provided in the AP
Current/Former Name(s) or Alias(es)	n/a	n/a	n/a

All supplies indicated in Table 6.1 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. Investigational Product

RSVpreF (PF-06928316) will be supplied in single use vials at a dose level of 120 mcg/vial powder for reconstitution for injection. Placebo will be supplied in single use vials of powder for reconstitution for injection. Bulk supplies of the Investigational product will be stored at [redacted] Pharmacy. The IMP must be stored according to the manufacturer's instructions.

Individual participant kits will be prepared by unblinded pharmacist for reconstitution with sterile Water for Injection (sWFI) and dispensing at site. A Qualified Person (QP) will release and deliver the Investigational product to hVIVO prior to administration of the vaccine to the participant. [redacted] Pharmacy and hVIVO will maintain drug accountability as detailed in the study-specific 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 study vaccine/placebo is monitored. 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 study vaccine/placebo.

6.2.2. 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 ºC 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 digit 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. A separate randomisation number will be allocated to the participants at randomisation and will be used for allocation of study intervention (RSVpreF or Placebo).

The randomisation number encodes the participant's assignment to receive RSVpreF or Placebo in a 1:1 ratio.

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

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

Randomisation numbers will follow a 3-digit format e.g., [001]. Participants who are replaced as per Section 7.4 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.

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. An independent Statistician [redacted] will prepare the randomisation schedule, and the IMP Manufacturer's pharmacist/designee [redacted] will prepare the participant level IMP doses in line with the randomisation schedule.

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 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.

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

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

The emergency code break envelopes will contain details of the treatment for each participant.

When the code break envelope is opened, the Investigator must note the date, time, reason for unblinding and the details of the investigator and or designated site staff that broke the blind and record this information according to hVIVO SOPs. The Investigator must also immediately notify the Sponsor's Medical Monitor (SMM) that the code has been broken. If possible, the Sponsor should be consulted before the code is broken, but this will only occur if the safety of the participant will not be compromised.

Even if the code is broken, blood samples for safety, efficacy 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 +155 (±14 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 Monitor (SMM), the medication will not interfere with the study procedures or compromise participant safetyMedications prohibited throughout the study are shown in Table 2.

Table 2 Prohibited Medication

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:

Prohibited medication	Washout
	•Chronically used medications, vitamins or dietary supplements, including any medication known to be moderate/potent inducers or inhibitors of CYP450 enzyme.
Any investigational medicinal product used in another trial	Within 3 months (or 5 half-lives of the investigational product used in the other trial), whichever is greater, prior to the planned date of viral challenge or dosing with IMP (whichever occurs first).

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 up to 7 days before the date of first dosing with IMP/viral challenge (whichever occurs first). 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 3 below:

Table 3 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.
If, e g in an outbreak or pandemic, a newly instated national vaccine program is applicable to an individual participant, the PI and sponsor will discuss on an individual basis if concomitant vaccination may be allowed, study vaccine/inoculation postponed or the participant withdrawn from 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.	

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 should be carried out, and if clinically indicated, the participant should be invited back for a final follow up visit.

The Sponsor should be notified of all study withdrawals in a timely manner, and in cases where the withdrawal is due to a medical reason the 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.

When the target evaluable participant number is achieved, for a given quarantine group or for the overall study, reserve vaccinated participants may not be inoculated with challenge virus. In addition to post vaccination visits (1 and 7 days post vaccination), participants may additionally have assessments performed on Day -2/-1/0 and the final follow up visit Day +155 (±14days) for safety and immunogenicity.

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 will be postponed until the 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 have been vaccinated but not inoculated may be replaced in order to achieve the planned evaluable number of participants if deemed appropriate by the PI and with the approval of the Sponsor.

The replacement participant will be assigned to the same group as the original (discontinued) participant. The replacement participant will be assigned a new, unique randomisation number equaling the randomisation number of the replaced participant, plus 100; for example, participant 001 would be replaced by participant 101). This will ensure that the replacement participant receives the same allocated blinded treatment as the participant who is being replaced.

7.5. Stopping Rules

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

Four 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 the Table 4 below:

Table 4 Study Stopping Rules

Status	Criterion	Procedure
1	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 SMM will review the data and make a decision on whether it is appropriate to recommence dosing or terminate the study. Regulatory authority approval via a substantial amendment would be required in order to recommence the study.
2	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 SMM 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 SMM will review the data and make a decision on whether it is appropriate to recommence inoculation or terminate the study. Regulatory authority approval via a substantial amendment would be required in order to recommence the study.
3	A serious adverse reaction (SAR) (i.e. a SAE considered at least possibly related to the IMP administration) has been reported in one participant.	If such a status occurs at any point during the study, then further administration of RSVpreF will not take place. The PI and the SMM will review the data and make decisions on whether it is appropriate to recommence dosing or terminate the study. Regulatory authority approval via a substantial amendment would be required in order to recommence the study.

Status	Criterion	Procedure
4	A severe non-serious adverse reaction (i.e. severe non-serious adverse events considered at least possibly related to the IMP administration) is reported in two participants, independent of whether or not within the same system-organ/class.	If such a status occurs at any point during the study, then further administration of RSVpreF will not take place. The PI and the SMM 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. Regulatory authority approval via a substantial amendment would be required in order to recommence the study.

In any event, participant follow-up should continue until resolution or stabilisation of AEs and final follow-up on Day +155 (± 14 days).

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8. Study Assessments and Procedures

Unless otherwise stated, study assessments will be performed according to hVIVO SOPs.

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 the Screening Visit

8.3. Height, Weight and Body Mass Index

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

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

8.4. 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.

8.5. Complete Physical Examination

A complete physical examination to include a full systemic assessment.

8.6. 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.

8.7. 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 millimetres of mercury (mmHg); measurements will be made supine. Where possible, the same arm will be used for all measurements.
- Peripheral arterial oxygen saturation (SpO_2%) 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 10.4 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 the United States Food and Drug Administration (FDA) Adult Toxicity Grading Scale for Preventive Vaccine Clinical Trials September 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.

8.8. Temperature

Body temperature will be measured by ether oral or tympanic route. The study specific normal range for temperature is detailed in Appendix 10.4.The severity of out of normal range values will be assigned using the FDA 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

Vaccine reactogenicity temperature monitoring will be recorded in the vaccine dairy card, as detailed in Section 8.11.1.

8.9. Electrocardiogram

Study specific normal ranges are provided in Appendix 10.4.

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.

8.10. Lung Function

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 difference 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.

8.11. Participant Diary Cards

8.11.1. Vaccination Diary Cards

Participants will be provided with a VDC, thermometer and calliper/ruler to measure and record local reactions and systemic events (including body temperature), for 7 days post-vaccination (Appendix 10.3). The diary card includes instructions on how to capture the data. Study site personnel are responsible for providing training for diary completion to avoid missing or incorrect data. Grading scales to assess severity of the symptoms are described in (Appendix 10.3).

Diary cards will be distributed on the day of vaccination (Day-28 (±3days)). Study site personnel will review the cards during the post vaccination visits (1 day and 7 days post-vaccination).

8.11.2. Symptom Diary Cards

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 diary card using a 100 mm scale, with the same symptoms, will be completed by the participants.

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

8.12. Questionnaires

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

PHQ-9 and GAD questionnaires will be used at the discretion of the Investigator to assess participants' eligibility in terms of ability to tolerate isolation in the quarantine unit.

8.13. 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 -1, with the first collection on Day 0. Thereafter distribution and collection of tissues will occur at 08:00h (± 1 hour). Tissues will be handed out daily and collection will occur until the discharge from quarantine.

In the event of a 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.

8.14. Urine Samples and Assessments

8.14.1. Urinalysis

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

Urinalysis will be performed to evaluate the parameters described in Appendix 10.2.

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.

8.14.2. Drugs of Abuse and Cotinine

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

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

8.14.3. 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.

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

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

8.15. Blood Samples

A maximum volume of 550 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.

8.15.1. Safety Blood Analysis and Assessments

Appendix 10.2 describes the safety blood tests that will be performed including, but not limited to, haematology, biochemistry, thyroid function test and cardiac enzymes. Additional safety assessments (e.g. coagulation) will be conducted at the discretion of the PI/Investigator, as required.

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

8.15.2. Challenge Virus Serology Samples

A participant must be sero-suitable to take part in the study; i.e. he/she must have low pre-existing serum levels of antibodies specific to the Challenge Virus. This antibody titer cut-off for serosuitability will be described in the AP.

8.15.3. Blood for Immunology Biomarker Evaluations

Blood will be taken for analysis related to the study exploratory endpoints. Immunology analysis will be performed in relation to the vaccine as well as viral infection and susceptibility, and may include, but not limited to:

- Serum for:
  - Humoral immune response (e.g. serum PreF and PostF IgG, IgA, sIgA, MNA)
  - Innate cytokines and chemokines response
  - Non-vaccine antigen-binding antibody assay for serological detection/seroconversion of community acquired RSV infection between vaccination and viral challenge.
- Whole blood for:
  - Genomics (e.g. HLA typing, SNPs, GWAS)
  - Transcriptomics (e.g. RNA-Seq, single cell RNA-Seq)
  - Cell mediated immunity (e.g. IFNγ T cell ELISPOT)
  - Cellular markers (e.g. Flow cytometry ICS, cytokine secretion from peptide stimulated PBMCs)

The detailed description of the assays performed in the study will be documented in the AP as appropriate.

8.16. Nasal Samples

The following upper respiratory sampling will be performed:

- Nasal sample (Nasopharyngeal swab or nasal wash) will be performed to collect samples of nasal cells and epithelial lining fluid for;
  - Respiratory Pathogen Screen
  - RSV discharge test
  - RSV quantification
  - Antibody binding and neutralisation assays
  - Exploratory purposes (remaining cells and epithelial lining fluid from the nasal samples may be stored for exploratory purposes).
  - Tolerance of the procedure may be determined at the screening visit.
- Nasosorption (Nasal wick) may be performed to collect epithelial lining fluid for assays such as:
  - Antibody binding and neutralisation assays
  - Proteomics (e.g. cytokines and chemokines)
  - RSV quantification
  - Transcriptomics
  - Exploratory purposes (remaining epithelial lining fluid may be stored for exploratory purposes).

8.16.1. Respiratory Pathogen Screen

On entry to quarantine, nasal samples will be collected and screened for the presence of respiratory pathogens, including SARS-CoV-2 virus, by multiplexed PCR-based methodology. A positive result from this pathogen screen 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 AP. Additional

test may be conducted if the results from the first test are invalid to support study eligibility prior to virus inoculation, or if a community acquired infection is suspected during quarantine.

A nasal sample might also be collected prior to vaccination on Day -28 to determine the presence of the SARS-CoV-2 virus.

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

8.16.2. Rapid Viral Antigen Test

A rapid diagnostic test (e.g. RVAT) will be used to determine the presence of RSV in a nasal 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 test result and/or the presence of clinical symptoms) A PCR screening test may be used as an alternative test for this purpose.

8.16.3. Viral Load

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

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

8.16.4. Biomarkers

The nasal sample and/or nasal wick (Class 1 Device) procedure may be used to collect samples of epithelial lining fluid (ELF) for:

- Antibody binding and neutralisation assays
- Proteomics (e.g. cytokines and chemokines)
- RSV quantification
- Transcriptomics
- Exploratory purposes (remaining epithelial lining fluid may be stored for exploratory purposes).

8.17. Recording of Adverse Events and Serious Adverse Events

The PI/Investigator is responsible for ensuring that all AEs, SAEs and pregnancies are identified, evaluated, recorded and reported in a timely manner as per Regulatory requirements and hVIVO's SOPs, and also for ensuring that the medical management (including follow up) of AEs, SAEs and, where appropriate, pregnancy symptoms/complications is provided by competent Investigator Site staff.

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.

8.17.1. 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.

8.17.2. 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.

8.17.2.1. Solicited AEs

Solicited AEs are pre-defined events for which participants are specifically questioned and which are noted by participants in their diaries (Section 8.11.1). Information related to solicited events as defined in Appendix 10.3 will be recorded by participants in a diary after vaccination. Each participant will be provided with a diary and instructions on how to complete the diary. There will be a minimum 30-minute post vaccination assessment of solicited events by the Investigator. The participant diary information will be transcribed by the study personnel in the appropriate eCRF pages. Participants will be asked to take a daily temperature measurement and to note in the diary occurrences of symptoms beginning on the evening of the study vaccine dosing day (on Study Day -28) and daily for the total of 7 days post-vaccination. Local reactions reported via the VDC are redness, swelling, and pain at the injection site. Systemic events reported via the VDC are fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain.

For all ongoing systemic events 7 days post vaccination, the stop date will be recorded in the CRF.

8.17.2.2. Unsolicited AEs

Unsolicited AEs are all AEs for which participants are not specifically questioned in the participant diary. Unsolicited AEs monitoring will begin after vaccination on the Vaccination (Study Day -28) Visit and will continue through 30 days post vaccination. Any unsolicited AEs that occurs after 30 days post-vaccination through to study completion will be recorded by the Investigator and included in the study database. Adverse events will be followed by the Investigator as specified in Section 8.17.3.

8.17.2.3. Medically Attended AEs

A medically attended adverse event (MAE) is an adverse event, whether considered related to the investigational vaccine or not, that led to the participant seeking evaluation by a healthcare provider. MAEs will be assessed between study day -28 and study Day +155 (6 months post-vaccination follow up), through self-report by participant and by query by the Investigator/designee at study visits and in any protocol specified telephone outreach.

8.17.3. 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. 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.

8.17.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator 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 the Sponsor's PV within 24 hours of becoming aware of the event
- Sponsor's PV will assess expectedness to determine if the SAE requires expedited reporting
- Sponsor's PV will send query to the PI if additional information is needed
- Sponsor's 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 will report SUSAR and other relevant safety information to the Ethics Committee in accordance with REC guidelines.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Research Ethics Committee (REC) and investigators.

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

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

In accordance with ICH GCP guidelines, the Sponsor will also inform the Investigator of findings that could affect adversely the safety of participants and/or impact the conduct of the trial. Annual safety reporting to the national Competent Authority (MHRA) and the Ethics Committee will be in agreement with ICH guideline E2F "Note for guidance on Development Safety Update Reports (DSUR)".

In addition, any other safety issue which may alter the current benefit-risk assessment of the IMP will be

reported by the Sponsor (or delegate) on an expedited basis to Competent Authorities, Ethics Committees and the Investigator.

The detailed procedure of the SAE/SUSAR reporting will be described in a Pharmacovigilance Management Plan that will be finalised before the start of the study to exactly define the different tasks of the Investigator, Sponsor and Sponsor's Pharmacovigilance vendor.

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

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

8.17.5. 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.

8.18. 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.

8.19. Biomarkers

Biomarkers may be evaluated from blood and nasal samples, as detailed in Section 8.15.3 and 8.16 respectively.

Samples may be used for exploratory biomarker research related to

- immunity and susceptibility to RSV infection
- RSV vaccine responses
- Immune response to RSV infection

8.20. Immunogenicity Assessments

Samples will be taken and assessed for immunological endpoints as detailed in Section 8.15.3 and 8.16 respectively. Samples may also be retained for future usage as described in Section 10.1.4.

9. Statistical Considerations

9.1. Statistical Hypotheses

S-cubed will perform the statistical analysis for the study. Full details of the planned statistical analysis will be presented in the Statistical Analysis Plan (SAP). Any deviations from the SAP will be documented in the Clinical Study Report (CSR).

9.2. Sample Size Determination

The statistical powering selected for this study is estimated to be sufficient for the primary objective and the primary endpoint family. The primary endpoint family consists of 3 endpoints listed below with their associated sample size estimates. As an exploratory proof of concept study, no adjustment for Type I error is planned in regard to the primary endpoint family. The sample size of 62 participants (31 in each group) will allow:

- Detection of a 70% relative reduction in the PCR-AUC virology with RSVpreF assuming a 96%CV in the control arm. The power for this endpoint is for 80% using a two-sided type-I error rate of 5%. The PCR-AUC data is based on log transformed PCR data.
- Detection of a 60% relative reduction in the symptomatic-infection rate with RSVpreF assuming a 59.26% rate in the control group (i.e. a rate of 23.7% in the RSVpreF group). The power for this endpoint is 80% using a two-sided type-I error rate of 5%. Symptomatic-infection is defined as:
    - Lab confirmed infection (two detectable (≥ Lower Limit of Detection LLOD) RT-PCR measurements (reported on 2 or more consecutive days), starting two days post-viral challenge (Day +2) up to discharge from quarantine), and
    - Either one or more positive clinical symptoms of any grade from two different categories in the symptom scoring system (Upper Respiratory, Lower Respiratory, Systemic), or one Grade 2 symptom from any category
- Detection of an 80% relative reduction in the total symptoms with RSVpreF assuming a 113.55% common CV. The power for this endpoint is at least 80% using a one sided type-I error rate of 5%.

The sample sizes indicate the number of vaccinated participants to be inoculated with the challenge virus per treatment group, more will be vaccinated in order to achieve the inoculation numbers. Therefore, up to 72 participants will be enrolled and vaccinated with the study vaccine, with 62 participants challenged with the study virus

9.3. Populations for Analyses

The following populations are defined:

Population	Description
ITTc (Intent-to-Treat-Challenge) Analysis Set	All participants randomly assigned to study intervention and who take a dose of study vaccine / placebo and were given viral challenge.

Per Protocol (PP) Analysis Set	All participants randomly assigned to study intervention and who take a dose of study vaccine / placebo, are given viral challenge, have no major protocol deviations, and who complete quarantine (Day 12).
Safety Analysis Set	All participants randomly assigned to study intervention and who take a dose of study intervention (study vaccine / placebo), regardless of whether they received the challenge virus or not. Participants will be analysed according to the intervention they actually received.

The primary analysis will be on the ITTc Analysis Set. Analysis using the PP Analysis Set will be secondary. The safety evaluation will be performed on the Safety Analysis Set.

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

9.4. Statistical Analysis

9.4.1. Sequence of Analysis

Two analyses will be conducted: the primary analysis after all participants have reached the Day 28 follow up, and a follow-up analysis at the end of the 6 months follow-up.

- The primary analysis will be performed when efficacy and safety clean data up to and including the study Day 28 visit are available from all participants. Before this analysis, the blinded data review will be conducted, the final SAP will be signed, and a formal database lock will take place. The list of study personnel with access to the result will be appropriately documented prior to unblinding. Appropriately defined study personnel will remain blinded (i.e., will not have access to the individual participant treatment assignment) until end of follow-up and final database lock. No individual listings mentioning individual participant treatment assignment will be released to the remaining study personnel until End of Study (EOS) and the Investigator will not have access to the treatment allocation up to study end and final database lock. The main analysis will be considered as final for key efficacy endpoints.
- The final EOS analysis will be performed when all endpoint data (safety and efficacy) up to study follow-up end (Month 6) are available and locked. All 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 SAP will provide a detailed description of the analyses that will be computed at the time of each analysis.

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 may be performed. These analyses may be documented separately to the CSR and may be made available to the Sponsor and Investigators at that time.

9.5. Statistical Analysis Plan

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

Primary and secondary efficacy endpoints will be descriptively summarised. Continuous variables will be summarised using a number of observations, mean (and/or geometric mean, where applicable), standard deviation, standard error, median, lower quartile, upper quartile, minimum and maximum values. Categorical variables will be summarised using proportions (counts and percentages).

Statistical analyses for the primary endpoint will be performed using appropriate one or two-sided hypothesis tests at the 5% significance level, with further details in the SAP. The t-test will be used to compare means between groups (and/or an appropriate alternative test, e.g. Wilcoxon Rank-Sum test, if the t-test assumptions are not satisfied). Methods for checking statistical model assumptions will be described in the SAP. Dichotomous data will be tested using a chi-squared test. No adjustment for the type I error is planned, as this is an early stage exploratory study.

The detailed SAP will be developed by S-cubed 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 the study expanding on the protocol specified analysis. Any deviation(s) from the original statistical plan should be described and justified in an amendment to the protocol and/or SAP as appropriate and referenced also in the final clinical study report (CSR). The SAP will describe and account for the occurrence of and extent of missing data, and its possible impact on the study analysis. All baseline assessments will be described in the SAP.

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

9.6. General Considerations

9.6.1. Participant Accountability

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

9.6.2. Protocol Deviations

Participants data will be reviewed for major protocol deviations prior to main analysis database lock at a planned blinded data review meeting (BDRM), and decisions will be documented within the meeting minutes. At this meeting, participants will be reviewed for their inclusion/exclusion from the analysis sets.

9.6.3. 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.

9.6.4. Compliance to Study Treatment

Compliance with study vaccine will be computed for each group as proportion of subjects received vaccine as randomised.

9.6.5. Primary Efficacy Analysis

The primary efficacy analysis of the primary endpoint family (as specified below) will be performed on the ITTc Analysis Set.

- The AUC for RSV-A Memphis 37b viral load measured in nasal samples by RT-qPCR, as determined by qRT-PCR on nasal samples collected twice daily starting two days post-viral challenge (Day +2) up to discharge from quarantine, will be summarised and RSVpreF compared to placebo via a t-test or Wilcoxon Rank-Sum test as appropriate.
- Symptomatic RSV infections will be summarised and RSVpreF compared to placebo using a chi-squared test. RT-PCR-confirmed symptomatic RSV infection, defined as:
    - RT-PCR-confirmed RSV infection (two detectable qRT-PCR measurements (reported on 2 or more consecutive days), starting two days post-viral challenge (Day +2) up to discharge from quarantine.), AND
    - Either one or more positive clinical symptoms of any grade from two different categories in the symptom scoring system (Upper Respiratory, Lower Respiratory, Systemic), or one Grade 2 symptom from any category.
- Sum total symptoms, as measured by graded symptom scoring system collected three times daily starting one days post-viral challenge (Day +1) up to discharge from quarantine, will be summarised and RSVpreF compared to placebo using a t-test or Wilcoxon Rank-Sum test as appropriate.

The primary efficacy analysis will be supported by sensitivity analyses and these will be specified in the SAP.

9.6.6. Secondary Efficacy Analysis

Secondary endpoints as described in Section 3 will be summarised by treatment group and analysed per Section 9.5 as appropriate.

9.6.7. Tertiary/exploratory Analysis

Except if otherwise specified, no formal statistical testing will be conducted for tertiary endpoints described in Section 3. Only the descriptive statistics will be computed. These analyses will be described in the SAP.

9.6.8. Safety Analyse(s)

Safety data will be summarised descriptively.

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

Solicited local and systemic AEs and unsolicited AEs will be summarised descriptively.

A by-participant 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 endpoints will be presented by treatment group includes laboratory evaluations (biochemistry, haematology, coagulation (if required), cardiac enzymes and urine analysis), vital signs assessments, physical examinations, 12-lead ECG and Spirometry. Additionally, physical examinations will be listed.

9.6.9. Other Analyse(s)

Certain pre-specified primary and secondary analysis (as documented in the SAP) will also be performed for the “Lab-confirmed infected” subgroup. The subgroup is defined as those participants that fulfil the following criteria:

- RT-PCR-confirmed quantifiable infection (two quantifiable RT-PCR measurements (reported on 2 or more consecutive days), starting two days post-viral challenge (Day +2) up to discharge from quarantine)

9.7. Interim Analyses

No interim analysis (i.e. an analysis of early trial data, before enrolment is completed, to detect trends that might warrant modification of the protocol, change in data being collected or trial termination) is planned for the study. A sequence of two analyses (primary analyses after the study Day 28 visit, and an EOS analysis after last participant last scheduled visit) is planned and described in Section 9.4.1.

The infection rate in the placebo group will be monitored on an ongoing basis by an unblinded statistician who does not have any other study function to confirm the powering assumptions (i.e. infection rate) within the Placebo group and ensure sufficient infection rate has occurred. If the infection rate is lower than anticipated, additional participants (up to 5 per treatment group) may be enrolled if needed to ensure the study is not underpowered.

The unblinded statistician will also monitor participant drop out between vaccination and inoculation to confirm that the number of participants inoculated in each treatment group is balance and 31 evaluable participants in each treatment group is achieved when the study is complete.

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

In addition to regulatory submission, the protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to a REC by the Investigator and reviewed and approved by the REC before the study is initiated.

Substantial amendments to the protocol will require Regulatory Authority approval prior to implementation. Any amendments to the protocol will require REC 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 REC annually or more frequently in accordance with the requirements, policies, and procedures established by the REC
- Notifying the REC of SAEs or other significant safety findings as required by REC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the REC, 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 vaccination visit (D-28 ±3 days) 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 vaccination visit, 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.

A separate ICF for genetic testing of samples will be required to document a participant's agreement to allow any specimens to be used for related exploratory genetic research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Storage of Samples for Future Research

Samples collected in this study may be stored for up to 25 years (or according to local regulations) for future research. The research may begin at any time during the study or the post-study storage period. Any movement and storage of samples will be in accordance with the Human Tissue Act 2004 and other relevant laws

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for future research.

10.1.5. Data Protection

Participants will be assigned a unique identifier by hVIVO. Any participant records or datasets that are transferred to the Sponsor’s collaborators 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 as well as the Sponsor collaborators and subcontractors in accordance with local data protection law. The level of disclosure must also be explained to the participant in ICF.

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 REC members, and by inspectors from regulatory authorities.

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. This can be paper source and/or eSource.

The Investigator must permit study-related monitoring, audits, REC 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.

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 for the study 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 and the Sponsor's collaborators. In addition, the site must conduct final disposition of all unused IMPs in accordance with the Sponsor and the Sponsor's collaborators. 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 and the Sponsor's collaborators.

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/she 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 the Sponsor's collaborators may jointly prepare and co-author manuscript(s) that could result from the clinical trial in accordance with the relevant contracts. Confirmation of study specific arrangements between Sponsor and Sponsor's collaborators can be found in the clinical study agreement.

10.2. Appendix 2: Clinical Laboratory Tests

[redacted]

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.

Table 5 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 (GGT) Alkaline phosphatase (ALP) Alanine transaminase (ALT) Lactate dehydrogenase

hVIVO template identifier: (G_0687) v3.0

Laboratory Assessments	Parameters
	Aspartate transaminase (AST) Urea.
Thyroid function	Thyroid Stimulating Hormone (TSH) at screening only Thyroxine at screening only
Cardiac enzymes	Creatine Kinase (CK) 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 clinically significant abnormal results)
Other screening/eligibility tests	Follicle stimulating hormone (FSH)* β-human chorionic gonadotrophin (β-hCG) Glycated haemoglobin (HbA1c) 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) Immunoglobulin A (IgA) antibodies

*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 investigator sites or other blinded personnel until the study has been unblinded, unless in the case of an emergency unblinding (Section 6.3).

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/expected viral symptoms on symptom diary cards • Procedural related events may be noted during the study whilst conducting nasal sampling (collection of nasal wash samples or nasopharyngeal swabs), specifically: ○ Nasal discomfort/irritation

- Nasal abrasions
- Nasal epistaxis
- Sneezing
- Watery eyes

When mild in nature and as expected in the opinion of the PI or Delegated Physician, these events will not be reported as adverse events.

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 assessed 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,

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

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 fulfills 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, diarrhea, 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 Investigator’s Brochure relating to the trial in question.

Medical events will be assessed for expectedness against the Reference Safety Information (RSI) section of the IB or equivalent, and any available IB addendum. Any changes to the RSI 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 time of written informed consent until study completion/final study contact or until the resolution of the AE. AEs will be fully recorded in the source documents as they

are reported, whether spontaneously volunteered by a 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.
Directed 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 SMM 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).

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 Investigator will use the FDA toxicity scale ["FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007."] 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 FDA toxicity scale should be determined according to the definitions in Table 6.

Table 6 Classification of Adverse Events Severity

Grade	Classification	Definition
Grade 1	Mild	Mild level of discomfort, and does not interfere with regular activities
Grade 2	Moderate	Moderate level of discomfort and significantly interferes with regular activities
Grade 3	Severe	Significant level of discomfort and prevents regular activities
Grade 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalisation or hospice care probable

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.

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 consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, 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 to Sponsor's Pharmacovigilance provider.

- 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 7:

Table 7 Classification if Adverse Events 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 8.

Table 8 Classification of Adverse Events 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 and REC reporting obligations for the study. If the Investigator does not have all of the details regarding the SAE he/she will not wait until this information becomes available before making the initial report to Sponsor. Contact details are detailed in Table 10.5.

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

All reports should be directed to the SMM. 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. The SAE reporting contact details will be included in the local study contact list document and the Pharmacovigilance/ Safety Management Plan.

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 and REC.

The Sponsor shall ensure that all relevant information about a SUSAR that occurs during the course of a clinical trial in the UK and is fatal or life threatening, is reported as soon as possible to the MHRA and the REC. This needs to be done within 7 calendar days after the Sponsor became aware of the event. Any additional relevant information should be sent within 8 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 study from ICF signature until last participant last scheduled visit must be reported by the Investigator to the SMM as soon as possible, in accordance with hVIVO's SOPs, and at the latest within 24 hours of becoming aware of the event.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of

the participant's participation in the study, must be followed-up until the event is considered resolved, until the participant is lost during follow-up, or until the PI in conjunction with the Sponsor deem the event stable and a decision for no further follow-up has been taken

10.3.11. Pregnancy

If a female participant or partner of a male participant becomes pregnant during the course of the study, this must be reported by the Investigator to the SMM 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 SMM 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.
- The emergency code break envelopes will be requested (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.

10.3.12. Reactogenicity Data

Reactogenicity data are solicited AEs collected using the VDC, starting on the day of vaccination through 7 days post vaccination. The reactogenicity data will include local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain).

10.3.12.1. Local Reactions

Local reactions reported in the VDC are redness, swelling, and pain at the injection site.

- **Presence of Local Reactions (Proportion of Participants Reporting)**

The participants will record the presence or absence of pain at the injection site in the diary as "Mild," "Moderate," "Severe," or "None." Redness and swelling will be measured in cm or measuring device units (range: 1 to 21 and 21+) and then categorised as mild, moderate, or severe based on the grading scale in Table 9. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. A participant with a severe (Grade 3 or above) local reaction will be prompted to contact the investigator to assess if an unscheduled visit is required to assess the reaction.

Table 9 Grading Scale for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis
Pain (at the injection site)	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalisation for severe pain at the injection site

Only an investigator is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or, in the case of pain at the injection site only, contact with the participant. If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the SMM. Grade 4 reactions will be recorded as an AE on the CRF.

The presence or absence of each local reaction on a given day is defined as follows:

= "Missing," if the value is missing on a given day;

= "Yes," if the participant reports the reaction as "Yes" for redness or swelling (with a diameter of more than 2.0 cm) **or** "Mild," "Moderate," "Severe," or "Grade 4" for pain at the injection site on a given day;

= "No," if the participant reports the reaction as "No" for redness or swelling **or** "None" for pain at the injection site on a given day.

For each local reaction, the derivation of whether or not the specific reaction occurred on "any day (Day 1-7)" will be made. The derivation of this variable is given in Table 10 below.

Table 10 Derived Variables for Each Local Reaction

Variable[a]	Yes (1)	No (0)	Missing (.)
Any day (Day 1-7)	Participant reports the reaction as "Yes" on any day from Day 1 through Day 7.	Participant reports the reaction as "No" on all 7 days or as a combination of "No" and missing on all 7 days.	Participant reports the reaction as missing on all 7 days.
a. The variable will be defined for each of the 3 local reactions.			

For "any local reaction" on any day, a similar definition can be applied, as given in Table 11 below.

Table 11 Derived Variables for Any Local Reaction

Variable	Yes (1)	No (0)	Missing (.)
Any day (Day 1-7)	Participant reports any redness or swelling >2.0 cm or "Yes" for pain at injection site on any day during Days 1 through 7.	Participant reports redness or swelling ≤2.0 cm or pain at injection site as "No" on all 7 days or as a combination of above and missing on all 7 days for all 3 local reactions.	Participant reports all of the local reactions as missing on all 7 days.

- **Maximum Severity for Local Reactions**

The maximum severity (highest grading) of each local reaction within 7 days after vaccination will be derived. The maximum severity will be derived as follows:

= "Missing," if values are missing for all days from Days 1 through 7;

= 0, if the participant reports all reactions as "No" or a combination of missing and "No" for all days from Days 1 through 7;

= *highest grade* (maximum severity) within 7 days after vaccination, if the answer is not "No" for at least 1 day.

- **Duration of Each Local Reaction**

The duration of each local reaction will be calculated in days as (resolution date of reaction - start date of reaction + 1). Resolution of the reaction is the last day on which the reaction is recorded in the VDC or the date the reaction ends if it is unresolved during the participant diary-recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing.

- **Onset of Local Reaction**

The onset day of each local reaction and any local reaction will be derived.

For the onset day of each local reaction, if participants report severity change for the local reaction, the first day of initial reporting of that specific local reaction will be counted.

For the onset day of any local reaction, the first day of reporting any severity of any local reaction will be counted.

In summary, the following variables will be derived for each local reaction:

1. Presence or absence of each local reaction on each day (Days 1-7) after vaccination.
2. Presence or absence of each local reaction on "any day (Day 1-7)" after vaccination.
3. Presence or absence of any local reaction on "any day (Day 1-7)" after vaccination.
4. Maximum severity of each local reaction on "any day (Day 1-7)" after vaccination.
5. Duration of each local reaction after vaccination.
6. Onset day of each local reaction after vaccination.
7. Onset day of any local reaction after vaccination

10.3.12.2. Systemic Events

Systemic events reported via the VDC are fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain. For all ongoing systemic events on Day 7, the stop date will be recorded in the CRF. Additionally, the participant is to document the presence or absence of systemic events in the VCD as "Mild," "Moderate," "Severe," or "None." Participants will assess the severity of each event according to Table 5.

Only an investigator is able to classify a participant's systemic event as Grade 4, after physical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or contact with the participant. If a participant experiences a Grade 4 systemic event, the

investigator must immediately notify the sponsor. A Grade 4 event will be recorded as an AE. The AE event will be graded as per Table 12.

Table 12 Grading Scale for Systemic Events

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4
Fatigue (= tiredness in diaries)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalisation for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalisation for severe headache
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalisation for severe vomiting
Nausea	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalisation for severe nausea
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalisation for severe diarrhea
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalisation for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalisation for severe joint pain

The highest temperature for each day for 7 days after vaccination is to be recorded in the VDC. For reporting purposes, fever will be analysed using the grading scale in Table 13.

Table 13 Grading Scale for Fever in the VDC

Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4
≥38.0°C to 38.4°C	>38.4°C to 38.9°C	>38.9°C to 40.0°C	>40.0°C

The presence or absence of each systemic event on a given day is defined as follows:

= "Missing," if the value is missing on a given day;

= "Yes," if the participant reports a temperature ≥38.0°C for fever **or** "Mild," "Moderate," "Severe," or "Grade 4" for the remaining events on a given day;

= "No," if the participant reports a temperature <38.0°C for fever **or** "None" for the remaining events on a given day.

For each systemic event, the following variables will be derived:

1. Presence or absence of each systemic event on each day (Days 1-7) after vaccination.
2. Presence or absence of each systemic event on "any day (Day 1-7)" after vaccination.
3. Maximum severity of each systemic event on "any day (Day 1-7)" after vaccination.
4. Presence or absence of any systemic event on "any day (Day 1-7)" after vaccination.
5. Duration of each systemic event after vaccination.
6. Onset day of each systemic event after vaccination.
7. Onset day of any systemic event after vaccination.

The derivation of these variables is similar to the derivation of the variables for local reactions (Section 10.3.13)

10.4. Appendix 4: Normal Ranges

Vital signs normal ranges

Vital signs	Lower limit	Higher limit	Units
Tympanic temperature (above 37.8 classed as pyrexia)*	35.5	37.8	oC
Oxygen saturation	Normal is ≥ 95		%
Respiratory rate	10	20	breaths per minute
Heart rate	40	100	beats per minute
Systolic BP	90	140	mmHg
Diastolic BP	60	90	mmHg

* Tympanic temperature refers to temperatures not recorded as part of the vaccine reactogenicity monitoring

ECG

ECG Parameters	Lower limit	Higher limit	Units
HR	40	100	bpm
QRS	60	120	ms
PR interval	120	220	ms
QT	320	450	ms
QTc	Normal for females is < 450		ms
	Normal for males is < 430		
QTcF	320	450	ms
QTcB	320	450	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 predicted value		litres

No single value should be used in isolation, all spirometry reference ranges require physician interpretation of the participant's overall status to determine their relevance.

10.5. Appendix 7: Abbreviations

Abbreviation	Term
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 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
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRP	C-reactive Protein
CV	Coefficient of Variance
CYP450	Cytochrome 450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECSC	European Coal and Steel Community
ELISA	Enzyme-linked Immunosorbent Assay
EU	European Union
FEV	Forced Expiratory Volume
FSH	Follicle Stimulating Hormone
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
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IM	Intramuscular
IMP	Investigational Medicinal Product
IUD	Intrauterine Device
LRT	Lower Respiratory Tract
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration

MCV	Mean Corpuscular Volume
MHRA	Medicines and Healthcare products Regulatory Agency
NIMP	Non-Investigational Medicinal Product
NPS	Nasopharyngeal Swab
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PFU	Plaque Forming Unit
PHQ	Patient Health Questionnaire
PI	Principal Investigator
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
SMM	Sponsor's Medical Monitor
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
TSS	Total Symptoms Score
UK	United Kingdom
URT	Upper Respiratory Tract
WBC	White Blood Cell
β-HCG	β-human chorionic gonadotrophin

10.6. Appendix 9: Definitions

10.6.1. General

TERM	hVIVO Services Limited Definition
Completion (of a participant's participation in the study)	A participant will be considered to have completed the study after his/her attendance at the last planned study visit, or the last unscheduled visit as applicable.
Baseline	For safety assessments the nearest assessments completed prior to vaccination will be used as the baseline measure, unless stated otherwise.
Enrolment (of a participant into the study)	A participant will be considered to be `enrolled` into the study once he/she has been randomised, dosed, or inoculated (whichever occurs first).
Infectious titre	The titre of virus inoculum producing viral infection in a participant. The term 'titre' applies to the quantity or concentration of virus inoculum (depending on the units documented).
Quarantine group	A group of participants who are admitted to and are resident in the Quarantine Unit for a particular quarantine period (i.e., participants whose Day 0 and scheduled discharge date are the same).
Quarantine period	The period of time when clinical trial participants are isolated in the Quarantine Unit during a HVC study.
Randomisation number	The number allocated to a participant at randomisation.
Participant number	The unique number assigned to a participant on the hVIVO participant database, which is used to identify the participant prior to randomisation.
Viral Challenge (or Challenge)	The inoculation of a participant with virus inoculum. By definition, the day of Viral Challenge is Day 0.

10.6.2. Study definition of infection and illness

TERM	CRITERIA
Seroconversion	Not applicable for RSV.

TERM	CRITERIA
Lower Respiratory Tract Illness (LRTI)	Any one of the following signs and/or symptoms on two consecutive scheduled assessments, at least one of which must feature Grade 2 severity, or if any of the following attain Grade 3 severity once: ○ Self-reported symptoms: cough, shortness of breath, chest tightness and wheeze ○ Physician findings: Abnormal breath sounds externally (e.g. stridor, wheezing) and on chest auscultation (rhonchi, crepitations or other).
Upper Respiratory Tract Illness (URTI)	Any one of the following signs and/or symptoms on two consecutive scheduled assessments, at least one of which must feature Grade 2 severity, or if any of the following attain Grade 3 severity once: Self-reported symptoms: rhinorrhoea (runny nose), nasal congestion (stuffy nose), sore throat, sneezing. Physician findings: nasal discharge, otitis, pharyngitis, sinus tenderness.
Systemic Illness	Fulfils the criteria for febrile illness, or fulfils the definition of upper respiratory tract illness and/or lower respiratory tract illness **And** Any one of the following symptoms on two consecutive scheduled assessments, at least one of which must feature Grade 2 severity, or if any of the following attain Grade 3 severity once • malaise • headache • muscles and/or joint ache • chilliness • feverishness
Febrile Illness	Any occurrence of temperature ≥ 37.9°C
Viral shedding	**One or both** of the following definitions must be met (between Day +2 and discharge from quarantine): • At least 2 positive quantifiable detections by viral load qPCR assay specific for the challenge virus, reported on 2 or more consecutive days and from 2 independent samples (which can either be the same type of sample or different e.g. throat swab and nasal wash or 2 nasal wash samples); • One positive detection by viral load qPCR assay, specific for the challenge virus, in which an aliquot of the same sample has also tested positive in a viral culture assay appropriate for detecting the challenge virus.

TERM	CRITERIA
Laboratory confirmed RSV infection	Viral shedding definition has been met.

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