CLINICAL STUDY PROTOCOL

A Phase 2a, Randomised, Double-blind, Placebo-controlled Study to Evaluate the Safety and Treatment Efficacy of SAB-176 (a Quadrivalent Anti-seasonal Influenza Immunoglobulin Product) in an H1N1 Challenge Model in Healthy Adult Participants

Short Title:	Phase 2a Influenza Human Challenge Study of SAB-176 in Healthy Adult Participants
Version and Date of Protocol:	Final Version 3.0. Date 13 Jul 2021
Sponsor Protocol Number:	SAB-176-201
hVIVO Protocol Number:	HVO-CS-008
Sponsor:	SAB Biotherapeutics, Inc. 2301 East 60th St. North, Sioux Falls, SD 57104 United States
Compound Number (if applicable):	SAB-176
EudraCT Number:	2021-001254-56

Confidentiality and Protections Statement:

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:

Rick Finnegan Chief Business Officer EVP, Program Management SAB Biotherapeutics	**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 United Kingdom (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): Victoria Parker

Institution and Address: hVIVO Services Limited

Queen Mary BioEnterprises Innovation Centre

42 New Road, London, E1 2AX, United Kingdom

Signature: _____ Date: _____

(DD MMM YYYY)

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

Study Personnel Contact Information

CONTACT	DETAILS
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Key Protocol Contributors	Refer to the local study contact list document

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
HVO-CS-008, V3.0	08 July 2021	The Protocol Amendment has been created to revise the below listed information. Infusion rate was amended to a stable rate of up to 2.0mL/min The incorrect timepoints in the SoA for randomisation and immune markers were amended from post- to pre-inoculation. Storage temperature of SAB-176/Placebo doses, which was inaccurate, was corrected. Additional information on blinding and randomisation process was added.
HVO-CS-008, V2.0	12 May 2021	Not applicable (first approved version).

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Protocol Amendment 01

Section / Title	Description of Change	Brief Rationale
1.2. Schedule of Activities (SoA): Randomisation	Randomisation timepoint was changed from Post-inoculation to Pre-inoculation.	The change was made to allow enough time for preparation, QP release and delivery of doses to investigational site.
1.2. SoA: Blood -immune marker	Time point for the immune marker was corrected from Post inoculation to Pre-inoculation	Blood immune marker time point was incorrect in the previous protocol version.
6.1. Table 2: Study Intervention	Vial concentration of SAB-176 was corrected in the Packing and Labeling section.	SAB-176 concentration from previous batch was left in the protocol by mistake and has been corrected.
6.2., 6.2.1. Interventional Product / Placebo	The infusion rate of interventional product was changed to a stable rate of up to 2.0mL/min.	Infusion rate was corrected based on the safety and tolerability profile of the Phase I study, with the highest administered dose of 50mg/kg. Dose level in this study is 25mg/kg.
6.2., 621. Interventional Product / Placebo	Storage temperature of SAB-176 / Placebo doses was corrected from 2°C-8°C to 15°C-25°C. Additional wording was added for clarity.	Storage temperature range 2°C-8°C relating to SAB-176 vials (bulk supplies) was incorrect for SAB-176 / Placebo doses which must be stored at 15°C-25°C.

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1. Protocol Synopsis

Phase	Phase 2a
Clinical Study Site	Single centre, hVIVO Services Limited
Indication	Treatment of influenza caused by Type A and Type B influenza viruses
Study Type	Interventional
Design	Up to 60 eligible participants will be randomized in a 1:1 ratio to receive either SAB-176 (up to 50 mg/kg dose) or placebo. Healthy adult participants will be pre-screened for serosuitability for Influenza A/California/2009 H1N1 challenge virus. Serosuitable participants who sign the study specific informed consent form (ICF) will be challenged with an intranasal administration of Influenza A/California/2009 H1N1 virus on Day 0. Participants will be given an intravenous (IV) infusion of SAB-176 or placebo on Day 1. Participants will be held in quarantine until Day 8.
Investigational Medicinal Product (IMP)	SAB-176 (a quadrivalent anti-seasonal influenza immunoglobulin product)
IMP dose	Single dose up to 50 mg/kg
Pharmaceutical form	Purified human immunoglobulin G (hIgG) in a sterile liquid formulated in 10 mM glutamic acid monosodium salt, 262 mM D-sorbitol, 0.05 mg/mL Tween 80, pH 5.5, administered as a liquid solution for injection in 0.9% sodium chloride (saline).
IMP route	Intravenous infusion
Control compound	Placebo
Randomisation	1:1 ratio active:placebo
Challenge virus	Influenza A/California/2009 H1N1 virus
Challenge virus route	Intranasal delivery
Challenge virus titre	Approximately 3.5 x 10^6 $\log_{10}$ tissue culture infectious dose ($TCID_{50}$)
Study population	Healthy male and/or female participants, between 18 to 45 years of age, pre-screened for serosuitability for Influenza A/California/2009 H1N1 challenge virus i.e., have levels of influenza antibodies compatible with susceptibility to influenza infection.
Summary of study design	This is an exploratory randomised, Phase 2a, double blind, placebo-controlled study to evaluate the safety and treatment efficacy

	of SAB-176 against Influenza A/California/2009 H1N1 virus infection in healthy adult participants. The study is divided into the following study phases: Screening phase: • Screening from 56 days (90 days for influenza serology) up to Day -3. Historical pre-screening data collected through the hVIVO Generic Screening process within 56 days (90 days for influenza serology) up to Day -3 may be transferred to this study after the study specific ICF has been signed by the participant. Inpatient phase: • Admission to the Quarantine Unit on Day -2 / -1; resident in the Quarantine Unit for approximately 11 days (e.g., from admission on Day -2 to planned discharge on Day 8). • Inoculation with Challenge virus on Day 0. • IV infusion with SAB-176 or placebo on Day 1. • Discharge from the Quarantine Unit planned on Day 8. Outpatient phase: follow-up visit: • Day 28 (±3 days).
Expected duration of participant participation	Approximately 5 weeks from signing study specific ICF to the participant's last scheduled visit.
Overall duration of clinical phase	The length of the clinical phase is estimated to last approximately 15 weeks from first participant first visit to last participant last visit.
End of study	The end of the study is defined as the date of the last scheduled visit of the last participant in the study.

Procedures and assessments	During the study, the following assessments and procedures will be performed:
	
	• Informed Consent
	• Eligibility Criteria
	• Medical & Medication History
	• Demographics
	• Height & Weight and Body Mass Index
	• Alcohol Breath Testing
	• Urine Sample Collection (safety, drugs of abuse, cotinine, pregnancy)
	• Complete Physical Examination
	• Directed Physical Examination
	• Vital Signs
	• Tympanic Temperature
	• Electrocardiogram
	• Spirometry
	• Symptom Diary Cards
	  ○ Categorical
	  ○ Visual Analogue Scale
	• Patient Health Questionnaire (PHQ-9)

	• Generalised Anxiety Disorder Questionnaire (GAD-7) • Wearable, if applicable • Inoculation with Challenge virus • IV Infusion SAB-176 or placebo • Nasal Discharge Collection • Blood Sample Collection • Nasal Sample Collection • Adverse events (AEs) and Concomitant Medications.
Sample size	Up to 60 participants will be inoculated with the Challenge virus. **Note**: A participant will be considered 'enrolled' into the study once he/she has signed the study specific ICF and eligibility is confirmed and has been inoculated with the Challenge virus. Potential participants who are screened under hVIVO generic screening process for the purpose of determining suitability for the study, but do not sign the study specific ICF to participate in the study, are not considered enrolled.
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 allocated blinded study intervention as the participant being replaced. The replacement participant will be assigned a new unique randomization number.
Statistics	**Sample size justification** Up to 60 participants will be inoculated with the Challenge virus. The statistical powering selected for this study is estimated to be sufficient for the primary objective and based upon only the primary endpoint. The targeted power for this study's endpoint is for 80% using a two-sided type-one error rate of 5%. The sample size of 60 participants (30 in each arm) will allow detecting a 60% relative reduction in the quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) area under the curve (AUC) virology with SAB-176 assuming an 81% coefficient of variation in the control arm. The PCR-AUC data is based on log-transformed PCR data. The sample size indicates the number of participants to be inoculated with the Challenge virus. **Primary efficacy analysis** The main estimator of the primary endpoint (the median area under the viral load-time curve [VL-AUC] of Influenza A/California/2009 H1N1 virus as determined by qRT-PCR on nasal samples [virology]), will be analysed on the Per Protocol (PP) Analyses Set. The calculation of the VL-AUC will be performed on log_{10}-transformed PCR data using the trapezoidal summation rule based on actual time intervals in hours.

	Descriptive statistics and the 95% confidence interval (CI) will be presented by treatment group. The difference between the two groups will be analysed using the Wilcoxon rank sum test. The two-sided p-value will be presented.

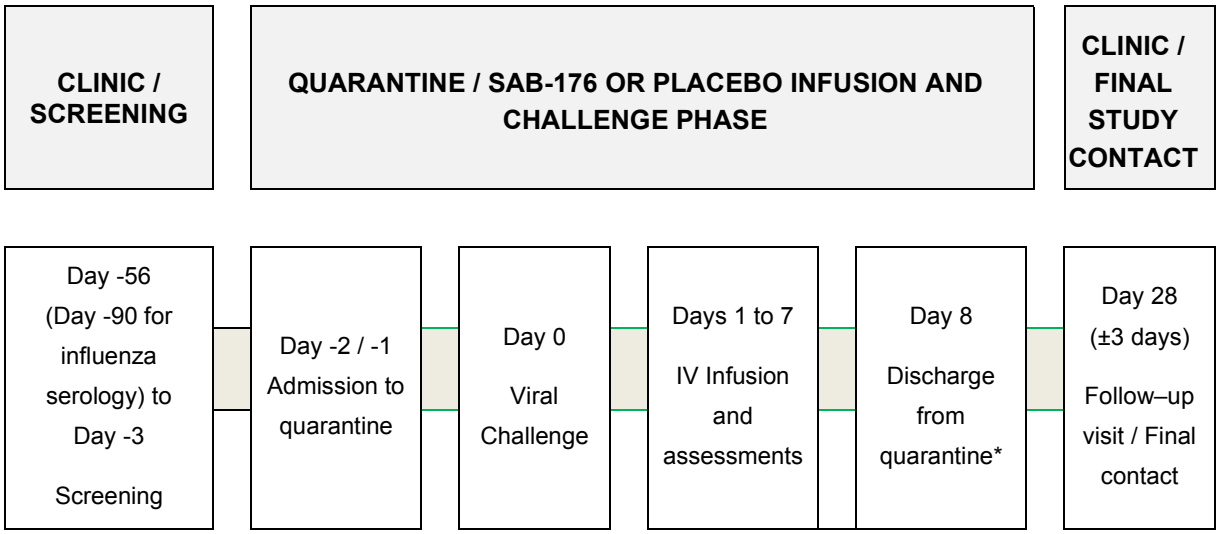
Objectives	Endpoints
Primary	
• To evaluate the effect of SAB-176, in reducing influenza viral load qRT-PCR when compared to placebo.	• Area under the viral load-time curve (VL-AUC) of Influenza A/California/2009 H1N1 virus, as determined by qRT-PCR on nasal samples.
Secondary	
• To further evaluate the effect of SAB-176, in reducing viral loads / viral shedding in qRT-PCR due to Influenza A/California/2009 H1N1 virus, compared to placebo.	• Peak viral load as defined by the maximum viral load determined by quantifiable qRT-PCR measurements. • Duration of influenza quantifiable qRT-PCR measurements.
• To evaluate the effect of SAB-176, in reducing viral loads / viral shedding in cell culture due to Influenza A/California/2009 H1N1 virus, compared to placebo.	• VL-AUC of Influenza A/California/2009 H1N1 virus, as determined by cell culture measurements. • Peak viral load as defined by the maximum viral load determined by quantifiable cell culture measurements. • Duration of influenza quantifiable cell culture measurements.
• To evaluate the effect of SAB-176, in reducing symptoms due to Influenza A/California/2009 H1N1 virus, compared to placebo.	• Area under the curve over time of total clinical symptoms score (TSS-AUC) as measured by graded symptom scoring system (categorical and visual analogue scales). • Peak symptom diary card score: peak total clinical symptoms (TSS) as measured by graded symptom scoring system (categorical and visual analogue scales). • Peak daily symptom score: Individual maximum daily sum of symptom score. • Number (%) of participants with Grade 2 or higher symptoms.

Objectives	Endpoints
• To evaluate the effect of SAB-176, in reducing the incidence of symptomatic infection due to Influenza A/California/2009 H1N1 virus, compared to placebo.	• RT-PCR-confirmed symptomatic influenza infection defined as: o RT-PCR-confirmed influenza infection, AND o Clinical symptoms. • Culture lab-confirmed reduction of symptomatic influenza infection defined as: o Lab-confirmed culturable influenza infection, AND o Clinical symptoms.
• To evaluate the safety of SAB-176, when compared to placebo.	• Occurrence of unsolicited adverse events (AEs) from IV infusion up to Day 28 follow-up. • Occurrence of serious adverse events (SAEs) from IV infusion up to Day 28 follow-up.
• To evaluate the safety of the Influenza A/California/2009 H1N1 virus challenge model.	• Occurrence of unsolicited AEs related to the viral challenge from viral challenge (Day 0) up to Day 28 follow-up. • Occurrence of SAEs related to the viral challenge from viral challenge (Day 0) up to Day 28 follow-up. • Use of concomitant medications from viral challenge (Day 0) up to Day 28 follow up.
Tertiary/Exploratory*	
• To further explore the effect of SAB-176, in reducing the incidence of influenza illness due to Influenza A/California/2009 H1N1 virus, compared to placebo.	• Upper Respiratory Tract illness, • Lower Respiratory Tract illness, • Systemic Illness, • Febrile Illness, • Mild to moderate symptoms.
• To explore the Minimal Clinically Important Difference (MCID) in instrument change (e.g., symptom diary cards).	• The average amount of instrument-assessed change for all participants who rate themselves as "a little better" or "somewhat better. • Additional endpoints may be considered for this objective and added at a later stage.

Objectives	Endpoints
• To explore the effect of SAB-176, in reducing the incidence of infection due to Influenza A/California/2009 H1N1 virus, compared to placebo.	• Influenza viral infection rates in upper respiratory samples by qRT-PCR and cell culture.
• To further explore the safety of the Influenza A/California/2009 H1N1 virus challenge model.	• Occurrence of haematological and biochemical laboratory abnormalities during the quarantine period.
• To explore the utility of wearable continuous monitoring for assessing Influenza A/California/2009 H1N1 virus infection/disease.	• Measures captured by continuous monitoring may be explored in relation to Influenza challenge.
• To explore genomic, transcriptomic, and immunological markers of Influenza A/California/2009 H1N1 virus infection, as well as the effect of SAB-176.	• Blood and respiratory samples may be investigated to assess i) the host baseline status, ii) response to infection, and iii) impact on SAB-176, for example: ○ Immune markers e.g., cytokines / chemokines, immunoglobulins ○ Deoxyribonucleic acid (DNA) (e.g., single nucleotide polymorphisms [SNPs], genome-wide association study [GWAS]) ○ Ribonucleic acid (RNA) transcriptomics (e.g., RNA sequencing, microarray) This is a non-exhaustive list.

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

1.1. Study Schematic: On-study Participant Progression



*NOTE: Release from quarantine is foreseen at Day 8 (8 days post-inoculation) in case no virus is detected by qualitative virus antigen test or polymerase chain reaction (PCR) (negative virus antigen test or PCR below Ct cut-off) and the participant has no clinically significant symptoms. If the participant continues to have clinically significant symptoms and/or detectable virus on Day 8, additional extended quarantine stay may be required at the discretion of the Investigator.

1.2. Schedule of Activities (SoA)

Study phase ➔	Screening phase*	QUARANTINE ISOLATION													Clinic visit	Early withdrawal visit
		Admission to quarantine		Human viral challenge (HVC)			Post HVC days							Discharge		
Study day ➔	Day -56 (Day -90 for influenza serology) to Day -3	Day	Day	Day 0			Day	Day	Day	Day	Day	Day	Day	Day	Follow-up	
Procedure ➔		-2	-1	Pre	Challenge	Post	1	2	3	4	5	6	7	8	Day 28 (± 3 days)	
Written consent (a)	X	X[o]														
Eligibility criteria (b)	X	X[o]		X												
Medical & medication history, and changes	X	X[o]														
Demographics	X															
Height & weight, and body mass index (BMI) (c)	X	X[o]												(X)	(X)	(X)
Alcohol breath test	X	X[o]													X	X
Urinalysis	X	X[o]												X	X	X
Urine drugs of abuse	X	X[o]													X	X
Urinary cotinine test	X	X[o]														
Urine pregnancy test (d)	X														X	X
Complete physical examination	X	X[o]												X	X	X
Directed physical examination (incl. nasal)				X		X	X[q]	X	X	X	X	X	X			
Vital signs (heart rate [HR], respiratory rate [RR], blood pressure [BP] systolic BP and diastolic BP, peripheral arterial oxygen saturation [SpO_2]) (e)	X	X[o]	TDS	TDS			8X	TDS	TDS	TDS	TDS	TDS	TDS	X	X	X
Tympanic temperature	X	X[o]	TDS	TDS			TDS[q]	TDS	TDS	TDS	TDS	TDS	TDS	X	X	X
Symptom diary card		X[o]	TDS	TDS			TDS[q]	TDS	TDS	TDS	TDS	TDS	TDS	X		
24-hour tissue count and nasal discharge (f)			X	X			X	X	X	X	X	X	X	X		(X)
12-lead electrocardiogram (ECG)	X	X[o]					X[r]		X				X		X	X
Spirometry (g)	X	X[o]							X				X		X	X

Study phase ➔	Screening phase*	QUARANTINE ISOLATION													Clinic visit	Early withdrawal visit
		Admission to quarantine		Human viral challenge (HVC)			Post HVC days							Discharge		
Study day ➔	Day -56 (Day -90 for influenza serology) to Day -3	Day	Day	Day 0			Day	Day	Day	Day	Day	Day	Day	Day	Follow-up	
Procedure ➔		-2	-1	Pre	Challenge	Post	1	2	3	4	5	6	7	8	Day 28 (± 3 days)	
Patient Health Questionnaire (PHQ-9)	X	X[o]														
Generalised Anxiety Disorder Questionnaire (GAD-7)	X	X[o]														
Wearable (continuous monitoring e.g., vital signs, temperature, ECG), if applicable	continuous[s]															X
Product Administration																
Challenge virus inoculation					X											
Randomisation				X		~~X~~										
Investigational medicinal product (IMP) / placebo dosing							X									
Collection of Blood Samples																
Serum follicle stimulating hormone (FSH) (h)	X															
Serum beta-human chorionic gonadotrophin (β-HCG) pregnancy test (i)		X[o]														(X)
Human immunodeficiency virus (HIV), Hepatitis A, B, and C tests	X															
Haematology (j)	X	X[o]					X[q]		X				X	(X)	X	X
Biochemistry (j)	X	X[o]							X				X	(X)	X	X
Coagulation (j)	X	X[o]					X[q]		X				X	(X)		X
Cardiac enzymes	X	X[o]							X				X			
Thyroid function test	X	(X)[o]														
Blood - immune markers (k)	X	X[o]	X	X			X[q]	X	X	X	X	X	X	X	X	X
Blood – transcriptomics markers			BD	X		X	BD[q]	BD	BD	BD	BD	BD	BD	X		

Study phase ➔	Screening phase*	QUARANTINE ISOLATION													Clinic visit	Early withdrawal visit
		Admission to quarantine		Human viral challenge (HVC)			Post HVC days							Discharge		
Study day ➔	Day -56 (Day -90 for influenza serology) to Day -3	Day	Day	Day 0			Day	Day	Day	Day	Day	Day	Day	Day	Follow-up	
Procedure ➔		-2	-1	Pre	Challenge	Post	1	2	3	4	5	6	7	8	Day 28 (± 3 days)	
Blood – deoxyribonucleic acid (DNA) - genomics		X[o]														
Blood - Pharmacokinetics (PK)		X[o]					2X[t]	X		X		X		X	X	X
Blood - anti-drug antibodies (ADA)		X[o]					2X[t]	X		X		X		X	X	X
Collection of Respiratory Samples																
Nasopharyngeal swab / nasal wash - Respiratory pathogen screen (l)	T	X[o]	(X)[p]													
Nasopharyngeal swab / nasal wash - Rapid viral antigen test or polymerase chain reaction (PCR)														(X)[p]		(X)
Nasopharyngeal swab / nasal wash – Virology (m) and exploratory research	T		X				BD[q]	BD	BD	BD	BD	BD	BD	X		X
Nasal sample (nasosorption / mid turbinate swab) – PK and exploratory immunology			X				X[q]	X	X	X	X	X	X	X		
Safety Assessments																
Adverse events (n)	X	continuous														X
Concomitant medications (n)	X	continuous														X

KEY NOTES FOR SCHEDULE OF EVENTS

X	Once
BD	Twice Daily. The timing of the baseline assessment will be the guide to establish the windows for subsequent measurements. For scheduling purposes, the baseline assessment will be defined as the first day when BD measurements are performed. Subsequent sampling / measures will be performed at the same time ±1 hour.
TDS	Three Times Daily. The timing of the baseline assessment will be the guide to establish the windows for subsequent measurements. For scheduling purposes, the baseline assessment will be defined as the first day when TDS measurements are performed. Subsequent sampling / measures will be performed at the same time ±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. Historical pre-screening data collected through the hVIVO Generic Screening process within 56 days (90 days for influenza serology) up to Day -3 may be transferred to this study after the study specific ICF has been signed by the participant.

a	Study specific consent may occur on the day of admission, providing all required eligibility information has been collected through hVIVO Generic Screening process.
b	Only the applicable Inclusion / Exclusion criteria will be reviewed at each time point.
c	Height will be taken at Screening only.
d	Urine pregnancy tests will be performed in female participants of childbearing potential.
e	Vital signs will be taken at the same time(s) each day (±1 hour). On Day 1 the vital signs will be performed pre-infusion, and at 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 4 hours, and 8 hours after the start of the drug infusion.
f	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 time points (±1 hour) with tissues distributed 24 hours ahead.
g	Assessments will be performed at the same time points (±1 hour) during quarantine.
h	A serum FSH test will be performed in all post-menopausal female participants.
i	Blood serum pregnancy test (β-hCG) will be performed in all female participants.
j	Blood may be drawn under non-fasted conditions. Repeat bloods may be drawn under fasted conditions if a lipid profile (triglyceride) or glucose is required (at Principal Investigators [PIs] discretion).
k	Blood will be collected for: i) virus serology (influenza antibody assay) to determine eligibility (at screening) and seroconversion (at Day -2 / -1 & Day 28), and ii) exploratory immune markers.
l	Nasopharyngeal swab or nasal wash for respiratory virus screen to assess for the presence of other respiratory viruses; if found positive the participant will not be eligible for the current quarantine.
m	Nasopharyngeal swabs (or nasal wash, if appropriate) will be collected for viral load assessments and exploratory immunology. Post inoculation nasal virology samples will be collected and used for qRT-PCR and viral culture assay.
n	Adverse events and concomitant mediations are reviewed throughout the study including pre- and post-infusion with IMP/placebo and pre- and post-inoculation.
o	Can be performed on Day -2 or Day -1. If admission at Day -1, all procedures scheduled for Day -2 can be performed on Day -1, as appropriate.
p	Optional and may be collected or not as per PI discretion for exploratory research.
q	Pre-infusion (only applicable to the first assessment on Day 1).
r	Post-dose ECG.
s	An exploratory wearable may be used to capture continuous measures parameters such as: HR, heart rate variability, SpO_2, temperature, ECG. This may include a period of up to 4 weeks prior to quarantine admission and up to 4 weeks post discharge from quarantine.
t	PK and ADA samples to be taken on Day 1 (IMP / placebo administration day): one sample pre-infusion and one sample at 1-hour post-infusion end (infusion end includes any time required for flushing).
Notes:	Parenthesis indicates the assessment may be optional, or at the PI's discretion. For all participants TDS assessments will commence on Day 0, the first assessment will be pre-virus challenge. The PI may perform additional safety assessments as required. Where any nasal sampling time points occur together, the order of sampling will typically be (1) nasosorption, (2) nasopharyngeal swab followed by (3) nasal wash

GENOMIC, TRANSCRIPTOMIC AND PROTEOMIC SAMPLES				
Deoxyribonucleic acid (DNA) / ribonucleic acid (RNA) / proteomic sample collection:	Yes	☒	No	☐
	DNA. RNA. Proteomics.			
Consent considerations:	Genetic consent. Future use of remaining samples for exploratory research: blood samples (including processed blood) and respiratory samples for biomarker analysis relevant to the exploratory objectives of the study.			

2. Introduction

SAB-176 is a purified human immunoglobulin G (hIgG) designed to specifically bind to Type A and Type B influenza viruses. The product is in development for use as a therapeutic agent to treat patients who are infected with Type A and Type B influenza viruses. The hIgG is purified from the plasma of immunized trans chromosomic (Tc) bovines that were immunized with a quadrivalent recombinant haemagglutinin (HA) protein vaccine produced in insect cells.

For more information on the non-clinical and clinical data regarding SAB-176, refer to the latest version of the Investigator's Brochure (IB Edition 1.2, 2021).

2.1. Background

Influenza causes substantial morbidity and mortality worldwide despite available antivirals and vaccines. Influenza is responsible for 226,000 excess hospitalizations and 30,000 to 50,000 deaths each year in the United States (US) alone (Thompson et al. 2003). Effective therapeutics are needed to prevent mortality or morbidity in those afflicted with severe influenza. Human plasma (delivered as Fresh Frozen Plasma units) or human intravenous immunoglobulin (hIVIg) with anti-influenza antibodies have been proposed as treatments for severe influenza (Luke et al. 2006). A limitation with plasma or hIVIg is that large numbers of human plasma donors/units must be screened to identify those few with a higher-than-average haemagglutination inhibition (HAI) titer to multiple strains of influenza. However, recent clinical trials have not shown benefit to hospitalized patients with severe Type A influenza infections treated with human-derived anti-influenza plasma or hIVIg (Beigel et al. 2019, Davey et al. 2019).

SAB Biotherapeutics, Inc., has developed SAB-176 to address the production limitations and lack of clinical efficacy of human-derived plasma or hIVIg. SAB-176 is a unique anti-influenza hIgG containing fully human polyclonal IgG antibodies with extremely high HAI and microneutralization titers against past, current, and potentially future strains of Type A influenza (H1N1/H3N2) and both lineages of Type B influenza (Yamagata/Victoria). SAB-176 is purified from the plasma of immunized Tc bovines that were immunized with a quadrivalent recombinant HA protein vaccine produced in insect cells. The HA antigens match the four influenza strains recommended yearly for the Northern hemisphere by the Center for Disease Control and Prevention.

Furthermore, Tc bovine hIgGs have an IgG1 subclass content of approximately 80-90% versus approximately 60% for human derived IVIg. IgG1 strongly activates complement and effector cells (natural killer cells, neutrophils, monocytes, etc.) of the innate immune system. SAB-176 is therefore much different than human-derived anti-influenza hIVIgs. SAB Biotherapeutics, Inc. believes that SAB-176's distinct attributes, in combination with early treatment of severe influenza disease, could demonstrate that the product reduces morbidity and mortality in patients with Type A and/or B influenza.

The genome of Tc bovines contains a human artificial chromosome comprising the entire human Ig gene repertoire (human Ig heavy chain [IgH] and human kappa light chain) that reside on two different human chromosomes (hChr), specifically the IgH locus from hChr14 and the immunoglobulin kappa (Igκ) locus from hChr2. The system maintains the ability to use the genetic information provided by the immunoglobulin gene repertoires for generating the seemingly unlimited diversity of human polyclonal antibodies (pAbs).

Fully hIgG (hIgG/hIgκ) can then be produced in these Tc bovines after vaccination with suitable antigens, and these animals produce up to 15 g/L of IgG antibodies in their plasma (similar to humans which have 7 to 16 g/L IgG). SAB-176 is an anti-influenza hIgG prepared in this system. Tc bovines receive repeated doses of a quadrivalent recombinant HA protein vaccine produced in insect cells. Just prior to immunization of the Tc bovine, the HA proteins are mixed with adjuvants.

Plasma is collected using an automated plasmapheresis system. After collection of sufficient volume, plasma undergoes Quality Control testing, is frozen and stored. Once it is ready to be processed, qualified frozen plasma is thawed, pooled, fractionated by caprylic acid and clarified by depth filtration in the presence of filter aid. The clarified sample containing hIgG is further purified by affinity chromatography, first using an anti-human IgG kappa affinity column to capture hIgG pAbs and remove residual non-hIgG and bovine plasma proteins. The sample is subsequently passed through an anti-bovine IgG heavy chain specific affinity column to further remove residual IgG molecules that contain a bovine heavy chain. The hIgG fraction is then subjected to a Q Sepharose chromatography polishing step to further reduce impurities, nanofiltration, final buffer exchange, concentration, and sterile filtration. Finally, the product is terminally filtered and filled into vials.

SAB-176 will be administered intravenously (IV) and will be diluted in saline.

2.2. Study Rationale

this study is to evaluate the safety and treatment efficacy of SAB-176 in a population inoculated with Influenza A/California/2009 H1N1 virus. This will both advance treatments for Type A and Type B influenza viruses, as well as establish the safety of the platform that could be used to quickly develop therapeutics for other emerging infectious diseases.

The Influenza A/California/2009 H1N1 virus challenge strain has been used for over 5 years by several groups globally and has helped assess influenza disease and therapies (Watson et al. 2015, Sloan et al. 2020). Specifically, hVIVO has direct experience with a range of H3N2, H1N1, and B influenza challenge viruses and have safety and inoculated over 1400 healthy participants, and specifically given over 100 participants a different batch of Influenza A/California/2009 H1N1 virus (Pleguezuelos et al. 2020).

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

2.3. Benefit/Risk Assessment

Healthy participants will not benefit from this clinical study. The study is designed to provide information about safety and efficacy of SAB-176.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of SAB-176 may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

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

2.3.1.1. Risks of SAB-176

SAB-176 is currently concluding a Phase 1 clinical trial (ClinicalTrials.gov identifier: NCT04471038). All participants have been infused with no serious adverse events (SAEs) reported through the highest dose cohort of 50 mg/kg and it appears to be safe and well tolerated. A previous Phase 1 study of SAB-301 (anti-Middle Eastern Respiratory Syndrome virus immunoglobulin) also derived from Tc bovines was shown to be safe and well tolerated at the highest dose of 50 mg/kg (ClinicalTrials.gov identifier: NCT02788188). It is anticipated that the risks for this Phase 2a study will be similar to the Phase 1 studies of SAB-176 and SAB-301 and the use of hIVIg with some unique considerations for proteins of animal origin as discussed below.

Based on hIVIg, common side effects may include:

- headache
- injection site reaction
- nausea
- urticaria
- fatigue
- arthralgia
- pyrexia.

Less common side effects may include:

- vomiting
- back pain
- rash.

Serious side effects seen with hIVIg that could be seen with SAB-176 include:

- Hyperproteinaemia, with resultant changes in serum viscosity and electrolyte imbalances may occur in patients receiving IVIg therapy (Steinberger et al. 2003). Humans routinely receive up to 1 to 2 grams/kg of hIVIg to treat Guillain-Barre syndrome and other immune related neuropathies. Therefore, the addition of 50 mg/kg IgG as SAB-176 is a relatively small amount and is unlikely to cause AEs related to increased viscosity.
- Aseptic Meningitis Syndrome has been reported with IVIg treatments, especially with high doses or rapid infusion. This risk is anticipated to be minimized given the low amount of protein and relatively slow infusion.
- Haemolysis, either intravascular or due to enhanced red blood cell (RBC) sequestration, can be seen with human IVIg. This risk is anticipated to be low given the lack of exposure of the cows to human RBC antigens.
- Volume overload has been reported with human IVIg. This risk is anticipated to be minimized given the low amount of protein and small total volumes administered.

There may be additional risks of SAB-176 given its animal origin. SAB-176 is a fully human IgG so it is anticipated the risk would be less, though there may be residual animal proteins. The most similar product would be Horse Heptavalent Botulism Antitoxin which is an equine derived non-human polyclonal IgG polyclonal:
(http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM345147.pdf),

There is the risk of off-target binding of the IVIg. In the worst case, this could cause immune activation (cytokine storm). The tissue cross reactivity assays do not predict any off-target binding, and this has not been seen in any other animal IVIg (of antigen-binding fragment [Fab]) preparations, so this risk is considered low.

For Horse Heptavalent Botulism Antitoxin, the most common adverse reactions (ARs) in all healthy participants were headache (9%), pruritus (5%), nausea (5%), and urticaria (5%). Other ARs reported in less than 4% of participants included pyrexia and throat discomfort. All reported ARs were considered mild or moderate. No serious ARs were reported. Two moderate acute allergic reactions that required premature termination of the infusion and treatment were reported. Reactions were predefined as mild if the participant was aware but could tolerate the symptoms. Moderate reactions were predefined as discomfort enough to interfere with normal daily activity.

The development of antibodies to bovine proteins and potential for food allergies is a theoretical concern. There is precedent for animal antibodies (or Fabs) being obtained from animal plasma and given to humans.

- Rabbit Anti-thymocyte Globulin [Thymoglobulin] (http://products.sanofi.ca/en/thymoglobulin.pdf).
- Horse Anti-thymocyte Globulin [Atgam] (http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM199603.pdf).
- Horse Heptavalent Botulism Antitoxin (http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM345147.pdf).
- Sheep Digoxin Immune Fab [DigiFab] (http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm117626.pdf).
- Sheep Digoxin Immune Fab [DigiBind] (http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=19044).
- Sheep Crotalidae Polyvalent Immune Fab [CroFab] (http://www.crofab.com/documents/CroFab-Prescribing_Information.pdf).

Upon review of these package inserts, the development of anti-drug antibodies (ADAs) was noted only in Horse Heptavalent Botulism Antitoxin (11 of 271 participants). There was no warning in any of these products concerning the development of allergies to other animal proteins, nor of any food allergies. As SAB-176 is a transgenic human IgG, the risk should be even further minimized. However, given that American / European diet is often heavy in bovine products (milk and/or beef, including derivatives), there is the risk of development of anti-bovine antibodies that is stimulated with repeated exposure. Given the data above and the lack of precedent for the development of food allergies after exposure to similar products, it is anticipated this risk with SAB-176 is very small.

Patients exposed to topical bovine thrombin products (previously used in surgical procedures e.g., fibrin glue) have developed antibodies towards bovine thrombin and contaminating bovine factor V; these antibodies can cross react with human clotting factors and may cause coagulopathy (Insight Flu IVIg Pilot Study Group 2016). In that series, postoperative coagulation abnormalities were more common in patients with antibodies to human coagulation proteins. SAB-176 clinical lots contain less than 5 ppm (parts per million) of bovine plasma proteins, but the clinical significance of this level of bovine contaminants is not known. Regardless, the serial assessment of prothrombin time/partial thromboplastin time (PT/PTT) in the study will monitor for any coagulation abnormalities in the participants receiving SAB-176.

As SAB-176 is bovine derived, it may contain galactose-alpha-1,3-galactose (alpha-Gal) glycosylation of the IgG. In other products, the alpha-Gal glycosylation has been shown to be the source of immune based hypersensitivity reactions. For example, the epidermal growth factor receptor inhibitor cetuximab is a monoclonal antibody with alpha-Gal glycosylation. Cetuximab, while a marketed product, has been associated with hypersensitivity reactions, including anaphylaxis. In most participants that had hypersensitivity reaction to cetuximab, IgE antibodies were present in pretreatment samples (Chung et al. 2008).

Lastly, SAB's Tc-bovine production system and the US cattle population have a negligible risk for transmissible bovine spongiform encephalopathy (BSE), also known as "Mad Cow Disease". Only three reported cases of BSE infection in cattle have been documented in the US in the last decade. Risk assessments for infectious diseases were completed on the production herd, and documented procedures are in place to reduce or eliminate certain infectious diseases in the production animals. All inputs (feed, medications, and vaccines) have been evaluated for the transmission of viral and BSE agents. The manufacturing process was also evaluated for the clearance and removal of viruses and BSE. Virus removal has been validated. The BSE Western blot analysis was done to demonstrate clearance and removal of prions.

There may be additional risks not apparent or predicted by preclinical testing.

2.3.1.2. Risks Associated with COVID-19 Pandemic

This clinical trial seeks to address the ongoing burden of severe Influenza infections worldwide, particularly in terms of hospitalisation and mortality, especially in clinically vulnerable groups, which remains ongoing during the covid-19 pandemic.

hVIVO implemented enhanced infection control measures during the pandemic to minimise risks of COVID-19 infection.

- Risk of increased severity of COVID-19 infection if contracted after challenge virus inoculation:

It has not been established that severity of COVID-19 infection could increase if contracted after inoculation.

Participants will be tested for respiratory pathogens, including COVID-19 on the arrival to the quarantine unit. They will be advised on protective measures and will need to follow infection control regimen.

- Risk of increased severity of COVID-19 infection after SAB-176 administration

There is no evidence that severity of COVID-19 infection would increase if contracted after SAB-176 administration. Participants will be tested for COVID-19 on the day of admission to the quarantine unit. They will be instructed on the infection control measures to follow.

All participants will be instructed to follow UK Government Covid-19 guidelines and will provided with Personal Protective Equipment (PPE).

COVID-19 related emerging data will be monitored ongoingly.

2.3.1.3. Other Risks

Table 1: Risk Assessment

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
Study procedures		
Intravenous (IV) Catheter	The primary risks of the placement of an IV catheter include local discomfort; occasional bleeding or bruising of the skin at the site of needle puncture; haematoma; and, rarely, infection or fainting.	The participant will be closely monitored and asked about these symptoms and before being allowed to stand up.
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 human immunodeficiency virus (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
Virus infection from inoculation		

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
Influenza A/California/2009 H1N1 virus infection and severe complications	Approximately 65% chance of becoming infected with Influenza A/California/2009 H1N1 virus (Sloan et al. 2020). Typical Influenza A/California/2009 H1N1 virus illness: abrupt onset of rhinitis, nasal stuffiness, fever, malaise, myalgia (muscle aches), and sore throat. Influenza, 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.	The safety profile of this batch of Influenza A/California/2009 H1N1 virus has been used for over 5 years by several groups globally. At hVIVO over 100 participants have been challenged with a different batch of Influenza A/California/2009 H1N1 virus. Influenza A/California/2009 H1N1 virus infection in healthy adults usually resolves without treatment within 3 to 7 days (Sloan et al. 2020). 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 8 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 (ECG) will be performed, and cardiac enzymes will be tested at least 3 days, and 7 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 Influenza A/California/2009 H1N1 virus to participants' close contacts	Influenza A/California/2009 H1N1 virus presence in nasal secretions can cause infection in close contacts.	Virus is usual absent from the nose by the time participants are discharged from quarantine. This will be confirmed by testing a nasal swab sample using by a qualitative virus antigen test or polymerase chain reaction (PCR) to determine

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
		participants' suitability for departure. In addition, participants will be instructed to avoid close contact with vulnerable people as described in Section 2.3.1.4 for two weeks after they leave the Quarantine Unit.
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.
Consult the Investigator's Brochure for detailed information on study intervention.		

2.3.1.4. 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).
    - 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).

2.3.2. Benefit Assessment

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

Participants may develop some immunity to Influenza A/California/2009 H1N1 virus and benefit from a general health check at Screening. Benefit may also be derived from the medical evaluations and

assessments associated with study procedures. In addition, participants are contributing to the process of developing new therapies in an area of unmet medical need.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants in this study, the potential risks identified in association with SAB-176 are justified by the anticipated benefits linked to the evaluation of SAB-176 in a viral challenge model of healthy adults, which will subsequently facilitate future assessment of influenza antibody therapies.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of SAB-176, in reducing influenza viral load quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) when compared to placebo.	• VL-AUC of Influenza A/California/2009 H1N1 virus, as determined by qRT-PCR on nasal samples.
Secondary	
• To further evaluate the effect of SAB-176, in reducing viral loads / viral shedding in qRT-PCR due to Influenza A/California/2009 H1N1 virus, compared to placebo.	• Peak viral load as defined by the maximum viral load determined by quantifiable qRT-PCR measurements. • Duration of influenza quantifiable qRT-PCR measurements.
• To evaluate the effect of SAB-176, in reducing viral loads / viral shedding in cell culture due to Influenza A/California/2009 H1N1 virus, compared to placebo.	• Area under the viral load-time curve (VL-AUC) of Influenza A/California/2009 H1N1 virus, as determined by cell culture measurements. • Peak viral load as defined by the maximum viral load determined by quantifiable cell culture measurements. • Duration of influenza quantifiable cell culture measurements.
• To evaluate the effect of SAB-176, in reducing symptoms due to Influenza A/California/2009 H1N1 virus, compared to placebo.	• Area under the curve over time of total clinical symptoms score (TSS-AUC) as measured by graded symptom scoring system (categorical and visual analogue scales). • Peak symptom diary card score: peak total clinical symptoms (TSS) as measured by graded symptom scoring system (categorical and visual analogue scales). • Peak daily symptom score: Individual maximum daily sum of symptom score. • Number (%) of participants with Grade 2 or higher symptoms.

Objectives	Endpoints
• To evaluate the effect of SAB-176, in reducing the incidence of symptomatic infection due to Influenza A/California/2009 H1N1 virus, compared to placebo.	• RT-PCR-confirmed symptomatic influenza infection defined as: o RT-PCR-confirmed influenza infection, AND o Clinical symptoms. • Culture lab-confirmed reduction of symptomatic influenza infection defined as: o Lab-confirmed culturable influenza infection, AND o Clinical symptoms.
• To evaluate the safety of SAB-176, when compared to placebo.	• Occurrence of unsolicited AEs from IV infusion up to Day 28 follow-up. • Occurrence of SAEs from IV infusion up to Day 28 follow-up.
• To evaluate the safety of the Influenza A/California/2009 H1N1 virus challenge model.	• Occurrence of unsolicited AEs related to the viral challenge from viral challenge (Day 0) up to Day 28 follow up. • Occurrence of SAEs related to the viral challenge from viral challenge (Day 0) up to Day 28 follow up. • Use of concomitant medications from viral challenge (Day 0) up to Day 28 follow up.
Tertiary/Exploratory*	
• To further explore the effect of SAB-176, in reducing the incidence of influenza illness due to Influenza A/California/2009 H1N1 virus, compared to placebo.	• Upper Respiratory Tract illness, • Lower Respiratory Tract illness, • Systemic Illness, • Febrile Illness, • Mild to moderate symptoms.
• To explore the Minimal Clinically Important Difference (MCID) in instrument change (e.g., symptom diary cards).	• The average amount of instrument-assessed change for all participants who rate themselves as "a little better" or "somewhat better. • Additional endpoints may be considered for this objective and added at a later stage.

Objectives	Endpoints
• To explore the effect of SAB-176, in reducing the incidence of infection due to Influenza A/California/2009 H1N1, virus compared to placebo.	• Influenza viral infection rates in upper respiratory samples by qRT-PCR and cell culture.
• To further explore the safety of the Influenza A/California/2009 H1N1 virus challenge model.	• Occurrence of haematological and biochemical laboratory abnormalities during the quarantine period.
• To explore the utility of wearable continuous monitoring for assessing Influenza A/California/2009 H1N1 virus infection/disease.	• Measures captured by continuous monitoring may be explored in relation to Influenza challenge.
• To explore genomic, transcriptomic, and immunological markers of Influenza A/California/2009 H1N1 virus infection, as well as the effect of SAB-176.	• Blood and respiratory samples may be investigated to assess i) the host baseline status, ii) response to infection, and iii) impact on SAB-176, for example: o Immune markers e.g., cytokines / chemokines, immunoglobulins o Deoxyribonucleic acid (DNA) (e.g., single nucleotide polymorphisms [SNPs], genome-wide association study [GWAS]) o Ribonucleic acid (RNA) transcriptomics (e.g., RNA sequencing, microarray) This is a non-exhaustive list.

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

4. Study Design

4.1. Overall Design

This is an exploratory randomised, Phase 2a, double blind, placebo-controlled study to evaluate the safety and treatment efficacy of SAB-176 against Influenza A/California/2009 H1N1 virus infection in healthy adult participants.

Up to 60 eligible participants will be randomized in a 1:1 ratio to receive either SAB-176 (up to 50 mg/kg dose) or placebo. Healthy adult participants will be pre-screened for serosuitability for Influenza A/California/2009 H1N1 virus challenge. Serosuitable participants who sign the study specific informed consent form (ICF) will be challenged with an intranasal administration of Influenza A/California/2009 H1N1 virus on Day 0. Participants will be given an IV infusion of SAB-176 or placebo on Day 1. Participants will be held in quarantine until Day 8.

The Study Schematic - showing participant progression through the study - is presented in Section 1.1; the Schedule of Activities (SoA) is presented in Section 1.2.

The total duration of study participation for a participant is approximately 5 weeks from signing study specific ICF to the participant's last scheduled visit, with the following sequence and duration of study phases:

- **Screening phase:** from 56 days (90 days for influenza serology) up to Day -3. Historical pre-screening data collected through the hVIVO Generic Screening process within 56 days (90 days for influenza serology) up to Day -3 may be transferred to this study after the study specific ICF has been signed by the participant.
- **Inpatient phase:** Participants will be resident in the Quarantine Unit for approximately 11 days (e.g., from admission on Day -2 to planned discharge on Day 8). Procedures will include:
    - **Pre-human viral challenge (HVC)**:
        - Admission to Quarantine Unit on Day -2 / -1.
    - **HVC**:
        - Inoculation with Challenge virus on Day 0.
    - **Post-HVC**:
        - IV infusion with SAB-176 or placebo on Day 1.
        - Day 1 to 7 onwards and each day – study assessments will be conducted as per SoA.
        - Participants will be discharged from the Quarantine Unit on Day 8 (or may remain longer at the Principal Investigator's [PIs] discretion).
- **Outpatient phase**:
    - Follow-up visit: Day 28 (±3 days).

4.2. Scientific Rationale for Study Design

4.2.1. Rationale for Study Design

The study will be conducted by hVIVO Services Limited, which has extensive experience with challenge studies. The Influenza A/California/2009 H1N1 virus strain has been shown to cause symptoms and virus shedding that closely match natural infection.

Administration of study intervention and challenge with Influenza A/California/2009 H1N1 virus will take place in hVIVO's specialised Clinical Units, either in the Quarantine Unit or Screening Clinic Units. Standard

study procedures (including collection of blood, urine, and nasopharyngeal secretions for assessment of safety and efficacy) have been employed in previous studies conducted by hVIVO.

The placebo control will be used to establish the frequency and magnitude of changes in endpoints that may occur in the absence of active treatment. Blinded treatment will enable the avoidance of bias in the interpretation of results.

Randomization will be used to minimize bias in the assignment of participants to treatment groups (active treatment or placebo), to increase the likelihood that known and unknown participant characteristics (e.g., demographic and baseline characteristics) are equally balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

4.2.2. Justification for Dose

A dose up to 50 mg/kg SAB-176 will be administered as a single IV infusion and is supported by the data of the previous clinical trial and the relevant non-clinical data for this investigational medicinal product (IMP). Based on the non-clinical toxicology results in New Zealand white rabbits, the no observed adverse effect level was 725.30 mg/kg/day or higher. The 725.30 mg/kg dose was the maximum dose available to test due to dose volume limitations for the species. Using body surface area calculations (FDA guidance for industry 2005) and 5X safety factor, a dose up to 50 mg/kg (the maximum therapeutic target dose for SAB-176) is equivalent to 770.8 mg/kg in rabbits.

4.3. 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 visit 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 SAE identified during the study period.

The end of the study is defined as the date of the last scheduled 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.

Up to 60 participants having passed both the hVIVO Generic Screening process and meeting the inclusion / exclusion criteria of the study and inoculated with Influenza A/California/2009 H1N1 virus on Day 0, will be randomised onto the study in a 1:1 ratio active:placebo.

5.1. Inclusion Criteria

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

NO	INCLUSION CRITERIA
1	An informed consent document signed and dated by the participant and the Investigator.
2	Aged between 18 and 45 years on the day of signing the study specific ICF.
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 follicle stimulating hormone (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 dosing with IMP. 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:

NO	INCLUSION CRITERIA
	i. combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: 1. Oral. 2. Intravaginal. 3. Transdermal. ii. progestogen-only hormonal contraception associated with inhibition of ovulation: 1. Oral. 2. Injectable. 3. Implantable. b. Intrauterine device. c. Intrauterine hormone-releasing system. 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 dosing with IMP: 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).* c. In addition, for female partners of childbearing 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 dosing with IMP.
7	Serosuitable to the Challenge virus, as defined in the study Analytical Plan (AP).

5.2. Exclusion Criteria

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

NO	EXCLUSION CRITERIA
Medical History	
1	History of, or currently active, symptoms or signs suggestive of upper or lower respiratory tract (LRT) infection within 4 weeks prior to the first study visit.
2	a) Any history or evidence of any other clinically significant or currently active systemic comorbidities including psychiatric disorders (includes participants with a history of depression and/or anxiety). b) And/or other major disease that, in the opinion of the Investigator, may put the participant at undue risk, or interfere with a participant completing the study and necessary investigations. *The following conditions apply:* • *Participants with clinically mild atopic eczema/atopic dermatitis and clinically mild psoriasis may be included at the Investigator's discretion (e.g., if small amounts of regular topical steroids are used, no eczema in cubital fossa; moderate to large amounts of daily dermal corticosteroids is an exclusion).* • *Rhinitis (including hay fever) which is clinically active or history of moderate to severe rhinitis, or history of seasonal allergic rhinitis likely to be active at the time of inclusion into the study and/or requiring regular nasal corticosteroids on an at least weekly basis, within 30 days of admission to quarantine will be excluded. Participants with a history of currently inactive rhinitis (within the last 30 days) or mild rhinitis may be included at the PI's discretion.* • *Participants with a physician diagnosed underactive thyroid who have been controlled on treatment for at least 6 months with evidence of a normal thyroid function test 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 resolved mild depression and/or anxiety 3 or more years ago 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 on admission. Participants with a history of stress related illness, which is not ongoing or requiring current therapy, with good evidence of preceding stressors may be included at the PI's discretion. All participants will be assessed prior to enrolment with a PHQ-9 and GAD-7 questionnaire.* • *Participants reporting physician diagnosed migraine, cluster headache/migraine or prophylactic treatment for migraine is an exclusion.* • *Participants with physician diagnosed mild irritable bowel syndrome not requiring regular treatment can be included at the discretion of the PI.*

NO	EXCLUSION CRITERIA
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 or body mass index (BMI) ≤18 kg/m^2 or ≥35 kg/m^2.
5	Females who: a) Are breastfeeding, or b) Have been pregnant within 6 months prior to the study.
6	History of anaphylaxis-and/or a history of severe allergic reaction or significant intolerance to any food or drug, as assessed by the PI.
7	Venous access deemed inadequate for the phlebotomy and cannulation demands of the study.
8	a) 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 hospitalised 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 within the 4 weeks prior to the planned date of viral challenge, unless medically necessary (e.g., during an outbreak or pandemic situation) and at the PI's discretion. b) Intention to receive any vaccination(s) before the day of Follow-up visit. (NB. No travel restrictions will apply after the Day 28 Follow-up visit). c) Receipt of influenza vaccine in the last 6 months prior to the planned date of viral challenge.
10	Receipt of blood or blood products, or loss (including blood donations) of 470 mL or more of blood during the 3 months prior to the planned date of viral challenge or planned during the 3 months after the final visit.
11	a) Receipt of any investigational drug within 3 months prior to the planned date of viral challenge. b) Receipt of three or more investigational drugs within the previous 12 months prior to the planned date of viral challenge. c) Prior inoculation with a virus from the same virus-family as the Challenge virus. d) Prior participation in another HVC 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. e) Receipt of a pAb or biologic within the previous 12 months prior to the planned date of viral challenge.

NO	EXCLUSION CRITERIA
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 HIV, active hepatitis A, B, or C test.
Other	
15	Those employed or immediate relatives of those employed at hVIVO or the Sponsor.
16	Any other finding that, in the opinion of the Investigator, deems the participant unsuitable for the study.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

No dietary restrictions are required before or after dose administration.

5.3.2. Caffeine, Alcohol, and Tobacco

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

Participants must not consume alcohol for 72 hours prior and during quarantine and for 72 hours prior to any study site 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 symptom 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 study site visit (unless it is within the usual activity of the participant) in order to avoid potential spurious elevation of clinical laboratory safety parameters.

5.3.4. Other Restrictions

Participants will be instructed to avoid close contact with vulnerable people as described in Section 2.3.1.4 for two weeks after they leave the Quarantine Unit.

5.4. Screen Failures

Screen failures are defined as participants who sign the study specific ICF but are not subsequently enrolled into the study.

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

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Study interventions administered to participants are described in Table 2.

6.1. Study Interventions Administered

Participants will be inoculated with an Influenza A/California/2009 H1N1 virus on Day 0. Participants will receive an IV infusion with SAB-176 or placebo on Day 1.

Table 2: Study Intervention

Intervention Name	SAB-176	Placebo	Influenza A/California/ 2009 H1/N1 virus
Type	Drug	Other	Virus
Dose Formulation	Purified hIgG in a sterile liquid formulated in 10 mM glutamic acid monosodium salt, 262 mM D-sorbitol, 0.05 mg/mL Tween 80, pH 5.5, administered as a liquid solution for injection in 0.9% sodium chloride	Sodium chloride 0.9% solution (normal saline)	Ampoule, Liquid
Unit Dose Strengths	Up to 50 mg/kg	Not applicable	The inoculum virus titre is determined in an infectivity assay, the titre is reported in tissue culture infectious dose ($TCID_{50}$) per mL ($log_{10}TCID_{50}$/mL). The challenge dose is approximately 3.5×10^6 $log_{10}TCID_{50}$.
Dosage Levels	A single dose up to 50 mg/kg	A single dose of 0 mg/kg	A single dose of virus will be delivered. Dose volume delivery method is provided in the AP.
Route of Administration	IV infusion	IV infusion	Intranasal
Use	Experimental	Placebo-comparator	Infectious challenge agent
IMP and Non-IMP	IMP	IMP (Placebo)	-
Challenge	-	-	Challenge virus

Intervention Name	SAB-176	Placebo	Influenza A/California/ 2009 H1/N1 virus
Sourcing	Sponsor	Provided centrally by HVIVO	Provided centrally by hVIVO
Packaging and Labelling	SAB-176 will be supplied in clear glass vials as a liquid purified hIgG in a sterile liquid formulated in 10 mM glutamic acid monosodium salt, with 262 mM D-sorbitol, and 0.05 mg/mL Tween 80, at a pH of 5.5. Each vial contains 74.17 mg / mL. The vials will be labeled and packaged in an outer vial box. Packs of up to 15 vials/boxes will be packaged together for ease of shipment/storage	Placebo (normal saline) will be supplied by the study site	Virus 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 or Alias	SAB 176	n/a	n/a

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Interventional Product / Placebo

SAB-176 is diluted in normal (0.9%) sterile saline under aseptic conditions. The diluted product is intended for administration by the IV route. The dose of IMP will be calculated. The pharmacy will prepare a bag containing the dose of SAB-176 plus as much normal (0.9%) saline as is needed to reach the concentrations for the study. The infusion of SAB-176 (active treatment) or normal saline control (placebo) will be provided in an opaque bag to obscure the bag (as SAB-176 may develop bubbles like IVIg if agitated). The drip chamber will also be covered, but accessible if needed by nursing staff for verification of flow rate, etc. The infusion will continue at a stable rate of up to 2.0 mL/min. Further details can be found in the Investigator's Brochure.

Participants randomised to the control (placebo) infusion will receive normal (0.9%) saline in approximately the same volume as they would have received if randomized to the active arm.

hVIVO will receive supplies of investigational product / placebo after it has had Qualified Person sign off by the Good Manufacturing Practice (GMP) Pharmacy provider and it has been verified ready for dispatch by the unblinded Study Monitor. All investigational product / placebo supplies will be used only for this protocol and for no other purpose.

Ready-to-dispense investigational product / placebo will be supplied by the pharmacy for each quarantine prior dosing. Once received at hVIVO, hVIVO will perform stock level accountability and the investigational product / placebo will be stored at 15 to 25ºC securely. Investigational product / placebo accountability will be controlled by hVIVO and monitored by the Study Monitor throughout the study and at study close-out.

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

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

6.2.2. Challenge Virus

Challenge virus inoculum will be prepared according to the hVIVO 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 Challenge virus stock, Influenza A/California/2009 H1N1, was manufactured under current GMP. The Challenge virus stock has undergone quality testing performed during manufacturing (identity, appearance, sterility, infectivity, and contaminants) according to pre-determined specifications, and has subsequently also passed an extensive panel of adventitious agent testing. The Challenge virus is stored in a secure -80°C freezer (normal temperature range -60°C to -90°C).

The time from the Challenge virus inoculum thawing to inoculation should be no longer than 4 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.

6.2.3. 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 study 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 study 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. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual or other specified location.

6.3. Randomisation and Blinding

hVIVO assigns a unique 6 digits number to each participant in the hVIVO database. This number will be used to identify a participant up to the point of randomisation, on source documents, on all study

correspondence and in the study database. A separate randomisation number will be allocated to the participants at randomisation and will be used for allocation of study intervention (SAB-176 or placebo).

A computer-generated randomisation schedule will be generated using SAS. Once assigned, that randomisation number shall not be reassigned.

Randomisation numbers will follow a 3-digit format e.g., [001]. A copy of the randomisation code list will be sent to the unblinded pharmacist preparing the study intervention, so that study intervention (SAB-176 or placebo) can be prepared for each participant as appropriate. The randomisation number encodes the participant's assignment to receive SAB-176 or placebo in a 1:1 ratio.

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

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

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

An individual access to a secured website will be provided to the Investigator. The website, compliant with 21CFR part 11 guidelines, will be used if unblinding is required. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make a reasonable attempt to contact the Sponsor prior to unblinding a participant's intervention assignment, provided that this would not delay emergency treatment of the participant. When the Investigator breaks the code, they will have to indicate on the website the reason for unblinding. The person who carried out the unblinding and the date and time of code breaking will be automatically recorded. After confirmation of the code break, the treatment allocation will appear on the screen. A notification with the treatment allocation will also be provided by email. A notification, without the treatment allocation, will be provided to the study team. Furthermore, the Sponsor must be notified within 24 hours after breaking the blind. Once the study is complete, the unblinded database will be provided to the Sponsor.

Even if the code is broken, blood samples for safety 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 study 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 at the study site 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 ICF, up to final study contact Day 28 (±3 days), will be recorded in the source data. Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrolment or receives during the quarantine/outpatient stage will be stored, prescribed and administered in line with their label-specific requirements, and recorded according to the parameters required by the clinical database.

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

Medications prohibited throughout the study are shown in Table 3.

Table 3: Prohibited Medication (Healthy Participants)

Prohibited medication	Washout
Systemic (oral and parenteral) antiviral drugs.	4 weeks prior to first study visit.
Influenza vaccine	6 months 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.	Within 7 days prior to the planned date of viral challenge: • Herbal supplements • Any medication or product (prescription or over the counter) for symptoms of nasal congestion • Short and long-acting antihistamines. Within 21 days prior to the planned date of viral challenge: • Chronically used medications, vitamins, or dietary supplements, including any medication known to be moderate/potent inducers or inhibitors of cytochrome P450 (CYP) enzyme.
Any IMP used in another trial	Within 3 months (or 5 half-lives of the IMP used in the other trial), whichever is greater, prior to the planned date of viral challenge.

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 viral challenge. During the study periods, the Investigator may permit a limited amount of paracetamol (no more than 4 g per day i.e., maximum daily dose) or topical medication, as clinically required for the treatment of headache or any other pain. Other medication to treat AEs may be prescribed if required.

Medications which are permitted throughout the study are shown in Table 4.

Table 4: Permitted Medication

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

6.6. Dose Modification

Not applicable.

7. Discontinuation of Study Intervention/Withdrawal

7.1. Participant Withdrawal

A participant may withdraw his/her 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 Influenza A/California/2009 H1N1 virus infection into the community, and to vulnerable groups in particular as described in Section 2.3.1.4.

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 and immunogenicity. 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.

Participants who are withdrawn from the study, will be requested to attend an Early Withdrawal Visit, with assessments as detailed in the SoA (Section 1.2).

7.2.1. Temporary Discontinuation / Temporary Delay in Enrolment

At the first study visit if a participant is found to be ineligible due to transient circumstances (such as acute disease and/or fever), dosing with IMP or inoculation 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 study site for a required study visit:

- The study 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.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

7.4. Participant Replacement Strategy

Participants may be replaced in this study.

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 allocated blinded study intervention as the participant being replaced. The replacement participant will be assigned a new unique randomization number.

7.5. Stopping Rules

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

Three clinical scenarios relating to the incidence of SAEs/suspected unexpected adverse reactions (SUSARs) during the study and the procedures that should be performed in each case are presented in the Table 5 below:

Table 5: Study Stopping Rules

Status	Criterion	Procedure
1	A report has been received of one (or more) SUSAR(s) in any, one (or more) participant(s).	If such a status occurs at any point during the study, then further administration of SAB-176 will not take place. The PI and the SME will review the data and make decisions on whether it is appropriate to recommence dosing (approval of a substantial amendment from the competent authorities is required) or terminate the study.
2	No SUSAR have been reported but an overall pattern of clinical changes or symptoms exists, attributed to the IMP, which may appear minor or moderate in terms of individual AEs, but which collectively represent a concern for safety.	If such a status occurs at any point during the study, then further administration of IMP will not take place. The PI and the SME will review the data and decide on whether it is appropriate to recommence dosing (approval of a substantial amendment from the competent authorities is required) or terminate the study.
3	Unexpected virus-related SAE or unexpected virus-related AEs of clinical concern have been reported following HVC. *Expectedness will be assessed by referring to the Challenge virus dossier.	If such a status occurs at any point during the study, then the PI and the SME will review the data and decide based on expectedness* of the viral event. If the event is unexpected, further administration of the virus will not take place. The PI and the SME will review the data and decide on whether it is appropriate to recommence inoculation (approval of a substantial amendment from the competent authorities is required) or terminate the study.

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

Further enrolment into the study may be either temporarily or permanently discontinued if:

- An unacceptable number of severe or life-threatening exacerbations take place (as determined by the PI).
- If two or more (or a group of participants) experience clinically significant life-threatening AEs that are deemed to be significant by the PI.

Development of a group or cluster of clinically significant AEs that represent a safety risk to participants that are deemed to be significant by the PI.

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 (Section 1.2). 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 nearest value obtained prior 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 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).

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 550 mL for any given 8-week period. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Medical and Medication History

Medical and medication histories including any allergies will be recorded at screening and on Day -2 / -1, including, but not limited to, detailed histories on allergies (e.g., rhinitis, dermatitis, food, aspirin / non-steroidal anti-inflammatory drugs and asthma).

8.2. Demographics

Demographic data will be recorded at screening.

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: $\text{BMI } (kg/m^2) = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$

8.4. Alcohol Breath Testing

Alcohol breath 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. Urine Samples and Assessments

8.5.1. 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 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.

8.5.2. Drugs of Abuse

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.

8.5.3. 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 female participants only.

8.6. Complete Physical Examination

A complete physical examination to include a full systemic assessment.

8.7. Directed 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 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.

8.8. 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.
- Blood pressure (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 4. If a result is out of the normal range and meets the criteria for an AE, the severity of the AE will be guided by the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007.

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

8.9. Tympanic Temperature

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

Temperature may be more frequently monitored in quarantine if appropriate.

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

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

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

8.10. Exploratory Wearables and Continuous Monitoring

Participants may be given the option to take part in a separate ethically approved exploratory non-interventional trial that aims to collect physiological data via a wearable device. Participants will have the wearable device trial explained to them and a choice to opt into the trial, which will require them to consent to wear a wearable device (such as a wrist-or armband during the challenge trial, via an additional informed consent, which will be separately ethically approved). There will be no impact on participants eligibility and/or safety follow-up or treatment in the challenge trial. The wearable device will not replace any conventional safety monitoring. All participants will be monitored for AEs related to the wearable device from signing of the wearable device ICF to the end of data capture. An AE related to the wearable device may lead to discontinuation of the exploratory wearable study, without having an impact on the human challenge trial.

8.11. Participant Diary Cards

Symptom Diary Card (Categorical and Visual Analogue Scale)

Participants will report and assess the severity of any Challenge virus-related symptoms 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 the time, and it stops me participating in activities: Shortness of Breath and Wheeze have an additional Grade 4: Symptoms at rest:

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

Additional to the categorical symptom diary card, a Visual Analogue Scale dairy card using a 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. 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 the same time points (±1 hour) with tissues distributed 24 hours ahead. 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.

8.13. Electrocardiogram

Study specific normal ranges are provided in Appendix 4.

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

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

8.14. Spirometry

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

Spirometry should meet the American Thoracic Society/European Respiratory Society guidelines criteria (Miller et al. 2005). For FEV1 and forced vital capacity (FVC), the highest value from a minimum of

three technically satisfactory attempts will be considered. For FEV1 and FVC the highest and the second highest value should not exceed more than 150 mL or 5% (whichever is greater). If the difference is larger, up to eight technically acceptable measurements will be made with repeatability assessed after each additional attempt. If after eight 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. FEV1 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.

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

8.15. Questionnaires

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

PHQ-9 and GAD-7 questionnaires will be used to assess participants' eligibility and current mental state regarding ability to tolerate isolation in the Quarantine Unit.

8.16. Blood Samples

A maximum volume of 550 mL of blood may be taken from each participant for any given 8-week period. 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.

8.16.1. Safety Blood Analysis and Assessments

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

Serum samples will be tested for serum FSH in post-menopausal female participants only and for serum pregnancy test in all female participants.

8.16.2. Challenge Virus Serology Samples

A participant must be serosuitable to take part in the study, i.e., he/she must have no or low pre-existing serum levels of antibodies specific to the Challenge virus. This antibody titre cut-off for serosuitability will be described in the AP.

Serum levels of pre-existing Virus specific antibodies to the Challenge virus will be determined using HAI influenza or as described in the AP.

8.16.3. Pharmacokinetic Blood Samples

Blood samples for determination of SAB-176 serum concentrations will be collected as outlined in the pharmacokinetic (PK) sampling schedule below:

Sampling schedule:

Day 1 (IMP / placebo administration day): one sample pre-infusion and one sample at 1-hour post-infusion end (infusion end includes any time required for flushing), and at Days 2, 4, 6, 8, and 28.

The allowable time windows for the sampling are as follows:

- ±5 minutes from the scheduled time for time points ≤1-hour post-infusion end.
- Allowable time windows from the scheduled time for time points >1-hour post-infusion end:
  - Day 2 timepoint (24 hours after infusion end): ±1 hour window.
  - Day 4 timepoint (72 hours after infusion end): ±2 hours window.
  - Day 6 timepoint (120 hours after infusion end): ±2 hours window.
  - Day 8 timepoint (168 hours after infusion end): ±2 hours window.
  - Day 28 timepoint (648 hours after infusion end): ±2 days window.
- There is no time window requirement for the pre-infusion sample. The pre-infusion PK sample must be taken on the same day prior to infusion.

Blood samples will be transported, processed, and stored in accordance with the AP. Pharmacokinetic analysis will be performed using HAI and neutralisation assays against the H1N1 strain at each participant collection timepoint. This analysis will be conducted at both hVIVO and Sponsor designated laboratories.

8.16.4. Anti-drug Antibodies

Blood (serum) samples will be collected to measure the incidence of ADAs to SAB-176 during the trial and follow the same sampling schedule for the PK blood samples as outlined in Section 8.16.3.

Blood samples will be transported, processed, and stored in accordance with the AP. ADA sample evaluations will be performed by the Sponsor designated laboratory.

8.16.5. Blood for Immunology Biomarker Evaluations

Blood may be used for exploratory analysis related to viral infection, for example:

- Genomics (e.g., GWAS, SNPs).
- Transcriptomics (e.g., microarray, RNA sequencing).
- Immunological markers (proteomics, cytokines, and chemokines)

8.17. Nasal Samples

Nasal sampling procedures will be performed for the following purposes during the study:

- Respiratory Pathogen Screen.
- Influenza discharge test.
- Viral load assays.
- Exploratory purposes:
  - Nasal PK
  - Viral resistance
  - Immunological markers.

Where any nasal sampling time points occur together the order of sampling will typically be (1) nasosorption or mid turbinate swab, (2) nasopharyngeal swab (3) nasal wash.

Tolerance of the nasal procedure(s) may be determined at the screening visit, as appropriate.

Remaining cells and epithelial lining fluid from the nasopharyngeal swabs may be stored for exploratory purposes.

8.17.1. Respiratory Pathogen Screen

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

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

8.17.2. Rapid Influenza Discharge Test

A rapid viral antigen test will be used to determine the presence of influenza only in a nasopharyngeal swab (or nasal wash) sample taken prior to discharge from the Quarantine Unit on Day 8. A qualitative PCR screening test may be used as an alternative test for this purpose.

8.17.3. Viral Load

Nasopharyngeal swabs (or nasal washes) will be collected for viral load assays. Viral load may be determined by qRT-PCR and a cell-based infectivity assay ($TCID_{50}$) if PCR positive, to investigate the following parameters:

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

8.17.4. Exploratory Analyses

8.17.4.1. Nasal Pharmacokinetics

Nasal sample aliquots (nasosorption / mid turbinate swab) may be processed, stored, and analysed for exploratory PK analysis in accordance with the AP.

8.17.4.2. Viral Resistance

A portion of each nasal sample may be processed, stored, and analysed for resistance analysis, in accordance with the AP.

8.17.4.3. Immunology

A portion of each nasal sample may be processed, stored, and analysed for immunological markers, in accordance with the AP.

8.18. 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 3.

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

All AEs / SAEs will be collected from the signing of the study specific ICF until the last follow-up visit at the time points specified in the SoA (Section 1.2).

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.

8.18.2. 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 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.

8.18.3. 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 3.

8.18.4. 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 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.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

An Investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the REC, if appropriate according to local requirements.

Further information on regulatory reporting requirements is provided in Appendix 3.

8.18.5. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected from signing study specific ICF onwards until the last study assessment as outlined in the SoA (Section 1.2). 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 3.

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

8.19. 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 Medicines and Healthcare Regulatory Agency (MHRA) and REC of the potential serious breach within 7 days of becoming aware of it.

8.20. Pharmacokinetics

Further details on PK sampling and analysis are outlined in Section 8.16.3 and 8.17.4.1.

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

8.21. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.22. Genetics

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

Details on processes for collection and shipment and destruction of these samples can be found in the AP.

9. Statistical Considerations

9.1. Statistical Hypotheses

The main study hypothesis is that treatment with SAB-176 will reduce the VL-AUC as determined by qRT-PCR in healthy adult participants after they have been challenged with Influenza A/California/2009 H1N1 virus when compared to treatment with placebo. The conclusions on efficacy will be based on the result of the primary analysis. Some other statistical tests will be performed for illustrative and exploratory purposes only. Consequently, no adjustment for multiplicity will be performed.

9.2. Sample Size Determination

Up to 60 participants will be inoculated with the Challenge virus.

The statistical powering selected for this study is estimated to be sufficient for the primary objective and based upon only the primary endpoint. The targeted power for this study's endpoint is for 80% using a two-sided type-one error rate of 5%. The sample size of 60 participants (30 in each arm) will allow detecting a 60% relative reduction in the qRT-PCR-AUC virology with SAB-176 assuming an 81% coefficient of variation in the control arm (taking into consideration Watson et al. 2015, Sloan et al. 2020).

The PCR-AUC data is based on log transformed PCR data.

The sample size indicates the number of participants to be inoculated with the Challenge virus.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Enrolled	All participants who signed the study specific ICF, their eligibility is confirmed, and have been inoculated with the Challenge virus.
Randomised	All enrolled participants randomly assigned to study intervention.
Intent to Treat (ITT) Analysis Set	All participants randomly assigned to study intervention who received the study intervention (SAB-176 or placebo).
The Intent to Treat Infected (ITT-I)	All participants randomly assigned to study intervention who received the study intervention and were infected with Challenge virus as per the definition of laboratory confirmed infection for this protocol
Per Protocol (PP) Analysis Set (or Evaluable set)	All participants randomly assigned to study intervention who received the study intervention (ITT Analysis Set participants) who have no major protocol deviation likely to impact the efficacy evaluation, and who complete the quarantine period up to the final day of quarantine, (Day 8).

Population	Description
Safety Analysis Set	All participants randomly assigned to study intervention and who received at least one dose of study intervention. Participants will be analysed according to the intervention they actually received.
PK Analysis Set	All participants randomly assigned to study intervention with at least three post-dose PK results.

The primary efficacy analysis will be on the PP Analysis Set. The ITT and ITT-I Analysis Sets will be used for supportive analyses on all or part of the primary and secondary efficacy endpoints, as defined in the Statistical Analysis Plan (SAP). The safety evaluation will be performed on the Safety Analysis Set. Additional analysis sets may be defined in the SAP.

9.4. Statistical Analyses

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

Venn Life Sciences will perform the statistical analyses for the study.

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

9.4.1. Statistical Analysis Plan

The SAP will be developed by Venn Life Sciences and approved by the Sponsor. The SAP will be finalised and signed prior to any look at unblinded of the data. The SAP will provide a more technical, detailed, and comprehensive description of the statistical analyses that will be computed, expanding on the protocol specified analyses.

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 trial report.

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

9.4.2. General considerations

9.4.2.1. Descriptive Statistics

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

Categorical variables will be summarised using number of available data, number of missing values, frequency counts for each category and corresponding percentage. Percentages will be calculated using the number of available data as the denominator (i.e., not including missing values). When relevant, CIs will be computed. If not otherwise specified in the SAP, the Wilson Score method will be used to compute CIs for proportions.

9.4.2.2. Inferential Statistics and Significance Testing

Between group comparisons will be performed using appropriate two-sided hypothesis tests at the 5% two-sided significance level, except if otherwise specified.

For continuous variables (either raw data or log-transformed data) the difference in means, the standard error and the 95% two-sided CI will be presented. In case of log-transformed variables, in addition to the previous statistics on the log-transformed data, the geometric means and geometric mean ratio and its 95% two-sided CI for the original variable will be presented. The Wilcoxon Rank-Sum test or the t-test or analysis of covariance will be used, depending on whether the endpoints are normally distributed. Details on the method used for each endpoint will be provided in the SAP. Methods for checking statistical model assumptions and alternative methods of analysis if the assumptions are not fulfilled will be described in the SAP.

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

9.4.3. Statistical Analysis

9.4.3.1. Participant Accountability

The number of participants receiving SAB-176 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 summarized.

9.4.3.2. Protocol Deviations

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

9.4.3.3. 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.

9.4.3.4. Compliance to Study Intervention

Compliance with study intervention will be computed for each participant as proportion of prescribed study intervention actually taken.

9.4.4. Primary Efficacy Analysis

The main estimator of the primary endpoint, the median VL-AUC of Influenza A/California/2009 H1N1 virus as determined by qRT-PCR on nasal samples (virology), will be analysed on the PP Analysis Set.

The calculation of the VL-AUC will be performed on log_{10}-transformed PCR data using the trapezoidal summation rule based on actual time intervals in hours. Results below the lower limit of quantification (LLOQ) will be given values as detailed in the SAP.

Descriptive statistics and the 95% CI will be presented by treatment group. The difference between the two groups will be analysed using the Wilcoxon rank sum test. The two-sided p-value will be presented.

The primary efficacy analysis will be complemented by the analyses of a supportive estimator (Median VL-AUC of Influenza A/California/2009 H1N1 virus as determined by quantitative viral culture) as well two sensitivity estimators:

- Geometric mean of VL-AUC of Influenza A/California/2009 H1N1 virus as determined by qRT-PCR.
- Geometric mean of VL-AUC of Influenza A/California/2009 H1N1 virus as determined by quantitative viral culture.

9.4.5. Secondary Efficacy Analysis

Table 6 summarises the methods for analysis of secondary endpoints. More details will be provided in the SAP.

Table 6: Methods for Analysis of Secondary Endpoints

Endpoints	Planned analysis
Peak viral load of VL-AUC of Influenza A/California/2009 H1N1 virus 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.	Wilcoxon-rank-sum test (alternative: t-test if underlying assumptions valid)
Duration of influenza quantifiable qRT-PCR measurements in nasal samples.	Wilcoxon-rank-sum test (alternative: t-test if underlying assumptions valid)
Area under the curve over time of total clinical symptoms score (TSS-AUC) as measured by graded symptom scoring system (categorical and visual analogue scales).	t-test if underlying assumptions valid (alternative: Wilcoxon-rank-sum test)
Peak symptoms diary card score: peak total clinical symptoms score (TSS) as measured by graded symptom scoring system (categorical and visual analogue scales).	t-test if underlying assumptions valid (alternative: Wilcoxon-rank-sum test)
Peak daily symptom score: Individual maximum daily sum of symptom score.	t-test if underlying assumptions valid

Endpoints	Planned analysis
	(alternative: Wilcoxon-rank-sum test)
Number (%) of participants with Grade 2 or higher symptoms.	Chi-square test
Incidence of symptomatic infection due to Influenza A/California/2009 H1N1 virus, compared to placebo as measured by: RT-PCR-confirmed symptomatic influenza infection defined as: • RT-PCR-confirmed influenza infection, AND • Clinical symptoms	Chi-square test (on the composite and each component)

9.4.6. Tertiary/exploratory Analysis

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

9.4.7. Safety Analyses

All safety analyses will be computed on the Safety Analysis Set.

Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated 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.

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

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

9.4.8. Pharmacokinetic Analysis

Blood PK analysis for SAB-176 will be performed using HAI and neutralisation assays against the H1N1 strain at each participant collection time point. This analysis will be conducted at both hVIVO and Sponsor designated laboratories.

PK parameters of interest may include:

C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, $t_{½}$

Pharmacokinetic parameters will be calculated using non-compartmental methods. Parameters will be summarised descriptively.

Exploratory nasal PK analysis may be performed, and parameters may be summarised descriptively.

9.5. 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.

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 International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- In addition to regulatory submission, the protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an REC by the Investigator and reviewed and approved by the REC before the study is initiated.
- 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 study 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 and for 1 year after completion of the study.

10.1.3. Informed Consent Process

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

When historical screening data collected through the hVIVO Generic Screening process is used for screening, the study specific ICF will be obtained at quarantine admission (Day -2 / -1) from each participant before any study specific procedures are performed.

Potential participants will typically be sent a copy of the ICF when their Screening Visit / Quarantine admission visit (as applicable) is arranged and at least a day prior to the visit and will be encouraged to

read it prior to their appointment. Upon arrival at the Screening Visit / Quarantine admission visit (as applicable), the ICF is discussed by the Investigator, and they will be given the opportunity to ask any questions and may take the information sheet away to consider their participation.

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

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

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

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

Participants may be given the option to take part in a separate ethically approved exploratory non-interventional trial that aims to collect physiological data which will require them to wear a wearable device via an additional informed consent, which will be separately ethically approved (for further details see Section 8.10).

10.1.4. Data Protection

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

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant 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.

10.1.5. Committees Structure

This study will not include an early safety data review. However, participant safety will be continuously monitored by the Sponsor’s internal/external safety review committee which includes safety signal detection at any time during the study.

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 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 study site using paper source casebooks which will then be data entered into the electronic CRF 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 study 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 electronic CRF 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**. In addition, the study site must conduct final disposition of all unused IMPs in accordance with **the Sponsor'**s procedures for the study.

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

10.1.10. Publication Policy

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

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 7 will be performed by the central laboratory.

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 7: 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 aminotransferase (ALT) Lactate dehydrogenase

Laboratory Assessments	Parameters
	Aspartate aminotransferase (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 (MCS) 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 A1c (HbA1c)** Total cholesterol 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 female participants
**Optional at PIs discretion

Investigators must document their review of each laboratory safety report.

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

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

10.3.1. Adverse Event

AE Definition
An AE is defined as any untoward medical occurrence in participants. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP, or for the purposes of HVC studies, the Challenge virus.

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

Events NOT Meeting the AE Definition

• Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE.
• Pre-existing disease or conditions present or detected prior to start of IMP or Challenge virus inoculation administration that does not worsen (including screening findings such as abnormal laboratory results).
• Hospitalisation for elective surgery, social and/or convenience admissions provided they are arranged before the start of IMP administration.
• Over-administration of either the Challenge virus, IMP or concomitant medication without any signs or symptoms.
• An uncomplicated pregnancy or an induced elective abortion to terminate a pregnancy without medical reason.
• Typical/normal viral symptoms on symptom diary cards
• Procedural related events may be noted during the study whilst conducting nasal sampling (collection of nasal wash samples or nasopharyngeal swabs), specifically:
  o Nasal discomfort/irritation
  o Nasal abrasions
  o 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 AEs.

10.3.2. Adverse Drug Reaction

An adverse drug reaction 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 adverse drug reactions. 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 AR, 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 IMP, 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 fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

• Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity. • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect.
f. Is an important medical event: • Important medical events' – some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered as 'serious' in accordance with the above definition. • Medical judgement should be exercised in deciding whether an AE/AR is serious. Important AEs/ARs 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 SUSAR is 'a serious AR, 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 section of the Investigator's Brochure or equivalent. Any changes to the Reference Safety Information will be deemed as a change to the risk/benefit profile and will require a substantial amendment to be submitted to the MHRA. This amendment must be approved before the changes are implemented in the study.

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

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

10.3.6.1. AE and SAE Recording

All AEs and SAEs will be collected from the 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, URT and LRT 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.

Assessment
Laboratory Values Deterioration in a laboratory value (compared to baseline) should only be reported as an AE if the deterioration fulfils the criteria for an AE. If deterioration in a laboratory result is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result will be considered as additional information. The Investigator and/or SME will judge whether abnormal laboratory values are clinically significant or not clinically significant, and record this in the source document. This entry should be signed and dated by the relevant Investigator. Laboratory abnormalities detected at screening will be considered as part of the medical history and will not be reported as AEs. Challenge virus associated laboratory abnormalities (e.g.: elevated ALT, AST or GGT; decreased neutrophils) may be recorded as AEs (at the discretion of the Investigator).
C-reactive Protein Any value above 5 mg/L but less than 60 mg/L will be a Grade 1 (mild) AE (unless deemed non clinically significant by the PI). The PI will use his/her clinical judgement to assign severity grades above Grade 1, based on evaluation of clinical signs and symptoms.

10.3.6.3. Assessment of Intensity

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

The Investigator will use the DMID toxicity scale 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 DMID toxicity scale should be determined according to the definitions in Table 8.

Table 8: 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 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 assesses causality for every event before the initial transmission of the SAE data.
- The Investigator may change his/her opinion of causality considering 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 9:

Table 9: Classification of 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.

Classification	Definition
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 ARs 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 10.

Table 10: 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 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 11.

- 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 SME. The Investigator at the study site is responsible for ensuring that a member of the Sponsor study team is made aware of any SAE reports that have been transmitted.

Table 11: Contact Details for Reporting All Serious Adverse Events

Contact	Details
Name of SME	Thomas C. Luke
SME SAE telephone number:	(240) 462 2505
Pharmacovigilance reporting email:	hvivo-clinical@arriello.com
Pharmacovigilance telephone reporting:	+370 37 247 987
SAE e-mail address:	tluke@sabbiotherapeutics.com

In addition, any AE resulting in permanent study discontinuation for a participant, even if not serious and regardless of expectedness or causality, must be reported by telephone, email, or fax to the Sponsor within 7 calendar days of the PI or any other study 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 study 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, serious ARs, or SUSARs (ARs, serious ARs, 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 the last participant last scheduled visit must be reported by the Investigator to the SME as soon as possible, in accordance with hVIVO's SOPs, and at the latest within 24 hours of becoming aware of the event.

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 SME 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 SME 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.

10.4. Appendix 4: Normal Ranges

hVIVO Normal Ranges for Healthy Participants

Vital signs normal ranges

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

ECG normal ranges

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

Spirometry normal ranges

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 5: Abbreviations

Abbreviation	Term
ADA	Anti-Drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
alpha-Gal	Galactose-alpha-1,3-Galactose
AP	Analytical Plan
APTT	Activated Partial Thromboplastin Time
AR	Adverse Reaction
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
β-hCG	β-human chorionic gonadotrophin
BD	Twice Daily
BMI	Body Mass Index
BP	Blood Pressure
BSE	Bovine Spongiform Encephalopathy
CI	Confidence Interval
CK	Creatine Kinase
CRF	Case Report Form
CRP	C-reactive Protein
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DMID	Division of Microbiology and Infectious Disease
ECG	Electrocardiogram
EU	European Union
Fab	Antigen-binding Fragment
FEV1	Forced Expiratory Volume in one second
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	Gamma Glutamyl Transferase
GMP	Good Manufacturing Practice
GP	General Practitioner
GWAS	Genome-wide Association Study
HA	Haemagglutinin
HAI	Haemagglutination Inhibition
HbA1c	Haemoglobin A1c
HbsAg	Hepatitis B Surface Antigen
hChr	Human Chromosomes
HepA	Hepatitis A Immunoglobulin M
HepC	Hepatitis C Antibodies
hIgG	Human Immunoglobulin G
HIV (1 / 2)	Human Immunodeficiency Virus (Type 1 / 2)
hIVIg	Human Intravenous Immunoglobulin
HR	Heart Rate
HVC	Human Viral Challenge
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IgA	Immunoglobulin A

IgH	Human Ig Heavy Chain
Igκ	Immunoglobulin kappa
IMP	Investigational Medicinal Product
ITT	Intent to Treat
ITT-I	Intent to Treat Infected
IV	Intravenous(ly)
LLOQ	Lower Limit of Quantification
LRT	Lower Respiratory Tract
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCID	Minimal Clinically Important Difference
MCS	Microscopy, Culture, and Sensitivity
MCV	Mean Corpuscular Volume
MedDRA	
MHRA	Medicines and Healthcare products Regulatory Agency
pAbs	Polyclonal Antibodies
PCR	Polymerase Chain Reaction
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
qRT-PCR	Quantitative Reverse Transcriptase-Polymerase Chain Reaction
RBC	Red Blood Cell
REC	Research Ethics Committee
RNA	Ribonucleic acid
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SME	Sponsor's Medical Expert
SNP	Single Nucleotide Polymorphism
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SpO_2	Peripheral Arterial Oxygen Saturation
SUSAR	Suspected Unexpected Adverse Reaction
T	Troponin
Tc	Trans Chromosomic
$TCID_{50}$	Tissue Culture Infectious Dose
TDS	Three Times Daily
T4	Free Thyroxine
TMF	Trial Master File
TSH	Thyroid Stimulating Hormone
TSS	Total Symptoms Score
UK	United Kingdom
US	United States
URT	Upper Respiratory Tract
VL-AUC	Area Under the Viral Load-time Curve
WBC	White Blood Cell

10.6. Appendix 6: 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 dosing 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 inoculated.
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 (RESPIRATORY SYNCYTIAL VIRUS, HEART RATE VARIABILITY AND INFLUENZA STUDIES)
Seroconversion	A ≥4-fold increase in Virus specific antibodies from baseline to follow-up post-quarantine
The following definitions should only be applied to data collected from Day 1 onwards	

TERM	CRITERIA (RESPIRATORY SYNCYTIAL VIRUS, HEART RATE VARIABILITY AND INFLUENZA STUDIES)
Lower Respiratory Tract Illness	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	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^{o}C (confirmed by a repeat measurement as ≥37.9^{o}C within 20 to 60 minutes).
Viral shedding	**One or both** of the following definitions must be met: • At least two positive quantifiable detections by viral load qPCR assay specific for the Challenge virus, reported on two or more consecutive days and from two independent samples (which can either be the same type of sample or different e.g., throat swab and nasal wash or two 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.
Laboratory confirmed Virus infection	Viral shedding definition has been met.

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