# CLINICAL STUDY PROTOCOL

**A Randomised, Double-blind, Placebo-controlled, Phase 2 Study to Assess the Safety, Tolerability, and Prophylactic Antiviral Activity against Influenza of Neumifil via a Human Viral Challenge Model in Healthy Adult Participants**

| | |
|---|---|
| **Short Title:** | Phase 2 study of the prophylactic antiviral activity of Neumifil in an influenza challenge model in healthy adult participants |
| **Version and Date of Protocol:** | Final Version 3.0, 12Feb2023 |
| **Sponsor:** | Pneumagen Limited<br>Kinburn Castle,<br>Doubledykes Road, St. Andrews, Fife,<br>Scotland, KY16 9DR |
| **Sponsor Protocol Number:** | PNG-NMF-201 |
| **hVIVO Protocol Number:** | [redacted] |
| **Compound:** | Neumifil |
| **EudraCT Number:** | 2022-001853-22 |

**Confidentiality and Protections Statement:**

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

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

## Sponsor Statement

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

## Sponsor Signatory:

| | |
|---|---|
| **Douglas Thomson** | **Date** |
| **Sponsor Representative, Pneumagen Limited** | (DD MMM YYYY) |

| | |
|---|---|
| **Geoff Kitson** | **Date** |
| **Sponsor's Medical Expert** | (DD MMM YYYY) |

## 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 study staff under my control.

## Principal Investigator Signatory:

Name (typed or printed): [redacted]

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 Staff Contact Information

| CONTACT | DETAILS |
|---|---|
| Sponsor | Pneumagen Limited<br>Kinburn Castle,<br>Doubledykes Road, St. Andrews, Fife<br>Scotland, KY16 9DR |
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| Study Design Lead: | [redacted]<br>hVIVO Services Limited,<br>Queen Mary BioEnterprises Innovation Centre,<br>42 New Road, London, E1 2AX, United Kingdom (UK)<br>Telephone: [redacted]<br>Email: [redacted] |
| Principal investigator and Clinical Study Unit | [redacted]<br>hVIVO Services Limited,<br>Queen Mary BioEnterprises Innovation Centre,<br>42 New Road, London, E1 2AX, United Kingdom (UK)<br>Telephone: [redacted]<br>Email: [redacted] |
| Sponsor's Medical Expert | [redacted]<br>Pneumagen Limited<br>Telephone: [redacted]<br>Email: [redacted] |
| Key Protocol Contributors | Refer to the local study contact list document |

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# 1. Protocol Synopsis

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| Protocol title | A randomised, double-blind, placebo-controlled, Phase 2 study to assess the safety, tolerability, and prophylactic antiviral activity against influenza of Neumifil via a human viral challenge model in healthy adult participants. |
| Short title | Phase 2 study of the prophylactic antiviral activity of Neumifil in an influenza challenge model in healthy adult participants |
| Protocol number | [redacted] (PNG-NMF-201) |
| Sponsor | Pneumagen Limited |
| Clinical phase | 2 |
| Study site(s) | hVIVO Services Limited,<br>Queen Mary BioEnterprises Innovation Centre,<br>42 New Road, London, E1 2AX, United Kingdom (UK)<br><br>hVIVO Services Limited<br>The Whitechapel Clinic (formerly The Whitechapel Hotel)<br>43-53 New Road, London, E1 1HH, United Kingdom (UK) |
| Study type | Interventional |
| Indication | Prevention of seasonal and pandemic influenza |
| Design | This is a proof-of-concept study to assess the efficacy and safety of a multiple dosing regimen (once daily for 3 days) and of a single dose of intranasal Neumifil, administered to healthy adults, initiated prior to being challenged with influenza A/Perth/16/2009 (H3N2) virus |

Objectives and endpoints

| | **Objective(s)** | **Related Endpoints/Outcome Measure(s)** |
|---|---|---|
| **Primary:** | *Efficacy* | |
| | To evaluate the effect of Neumifil in 1) reducing the incidence of symptomatic influenza infection and/or 2) reducing the severity of symptoms after influenza viral challenge, compared to placebo. | The study has 2 primary endpoints:<br><br>1) Reducing the incidence of symptomatic influenza infection:<br><br>• Reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed symptomatic influenza infection, defined as:<br><br>○ RT-PCR-confirmed influenza infection defined as 2 detectable (≥ lower limit of detection [LLOD]) RT-PCR measurements (reported on 2 or more independent nasal samples |

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| | | over 2 days), starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am),<br>AND<br>○ Any symptoms of grade ≥2 at a single time point.<br>2) Reducing the severity of symptoms:<br>• Peak symptoms diary card score: peak total symptoms score (TSS) as measured by graded symptom scoring system collected 3 times daily, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am). |
| **Secondary:** | *Efficacy* | |
| | To evaluate the effect of Neumifil in reducing clinical symptoms due to influenza viral challenge, compared to placebo. | • Area under the curve over time of total symptoms score (TSS-AUC) as measured by graded symptom scoring system collected 3 times daily, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am).<br>• Peak daily symptom score: individual maximum daily sum of symptom score, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am).<br>• Number (%) of participants with grade 2 or higher symptoms, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am).<br>• Duration of clinical symptoms: 1) any symptoms, 2) TSS of 2 or more (with at least 2 systems), and 3) grade 2 or higher symptoms, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am).<br>• Time to resolution from peak clinical symptoms as measured by graded symptom scoring system collected 3 times daily. Time to resolution is defined as the time (hours) from peak clinical symptoms until first time with TSS = 0 after which no further increase above 0 is observed. |
| | To evaluate the effect of Neumifil in reducing or shortening viral shedding after influenza viral challenge, compared to placebo. | • Area under the viral load-time curve (VL-AUC) of influenza challenge virus as determined by quantitative RT-PCR (qRT-PCR) on nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am).<br>• VL-AUC of influenza challenge virus as determined by tissue culture on nasal samples, starting from Day 1 (pm) up to |

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| | | | planned discharge from quarantine (Day 8, am).<br>• Peak viral load (VLPEAK) of influenza as defined by the maximum viral load determined by qRT-PCR measurements in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am).<br>• VLPEAK as defined by the maximum viral load determined by quantitative viral culture measurements in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am).<br>• Duration of quantifiable influenza, assessed by qRT-PCR measurements in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am). Duration is defined as the time (hours) from first quantifiable until first confirmed unquantifiable assessment after their peak measure (after which no further virus is quantified).<br>• Duration of detectable influenza, assessed by qRT-PCR measurements in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am). Duration is defined as the time (hours) from first detectable until first confirmed undetectable assessment after their peak measure (after which no further virus is detected).<br>• Duration of quantifiable influenza viral culture measurements in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am). Duration is defined as the time (hours) from first quantifiable until first confirmed unquantifiable assessment after their peak measure (after which no further virus is quantified).<br>• Duration of detectable influenza viral culture measurements in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am). Duration is defined as the time (hours) from first detectable until first confirmed undetectable assessment after their peak measure (after which no further virus is detected).<br>• Time to resolution from VLPEAK as defined by the maximum viral load determined by qRT-PCR measurements in nasal samples. Time to resolution is defined as the time (hours) from VLPEAK until first confirmed undetectable | |

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| | | assessment (after which no further virus is detected).<br>• Time to resolution from VLPEAK as defined by the maximum viral load determined by qRT-PCR measurements in nasal samples. Time to resolution is defined as the time (hours) from VLPEAK until first confirmed unquantifiable assessment (after which no further virus is quantified).<br>• Time to resolution from VLPEAK as defined by the maximum viral load determined by viral culture measurements in nasal samples. Time to resolution is defined as the time (hours) from VLPEAK until first confirmed undetectable assessment (after which no further virus is detected).<br>• Time to resolution from VLPEAK as defined by the maximum viral load determined by viral culture measurements in nasal samples. Time to resolution is defined as the time (hours) from VLPEAK until first confirmed unquantifiable assessment (after which no further virus is quantified). |
| | To evaluate the effect of Neumifil in reducing nasal discharge, compared to placebo. | • Total weight of mucus produced, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am).<br>• Total number of tissues used by participants, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am). |
| | To evaluate the effect of Neumifil in reducing the incidence of influenza infection due to influenza viral challenge, compared to placebo. | • RT-PCR-confirmed influenza infection, defined as 2 quantifiable (≥ lower limit of quantification [LLOQ]) qRT-PCR measurements (reported on 2 or more independent nasal samples over 2 days), starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am).<br>• Occurrence of at least 1 positive quantitative (≥ LLOQ) cell culture measurement in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am).<br>• Culture lab-confirmed symptomatic influenza infection, defined as:<br>  ○ Lab-confirmed culturable influenza infection (1 quantifiable [≥ LLOQ] cell culture measurement, starting from Day 1 [pm] up to planned discharge from quarantine [Day 8, am]), |

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| | | | AND<br>○ Any symptoms of grade ≥2 at a single time point.<br>Further sensitivity analysis may be performed on the above qRT-PCR-related endpoints where detection by qRT-PCR is reported above the LLOD instead of the LLOQ and/or using other definitions for the symptomatic component. Details will be provided in the statistical analysis plan (SAP).<br>• Number (%) of participants with lab-confirmed infection and fever (≥37.9°C). |
| | | *Safety* | |
| | | To evaluate the safety of intranasal doses of Neumifil, compared to placebo. | • Occurrence of adverse events (AEs) (solicited and unsolicited) up to the Day 28 (±3 days) follow-up visit, including any serious adverse events (SAEs).<br>• Occurrence of unsolicited AEs of special interest (AESIs) up to the Day 28 (±3 days) follow-up visit. AESIs are: clinically significant reduction in forced expiratory volume in 1 second ($FEV_1$) and forced vital capacity (FVC). |
| | | To monitor the safety of the challenge virus. | • Occurrence of unsolicited AEs related to virus challenge from Day 0 up to planned discharge from quarantine (Day 8, am).<br>• Occurrence of unsolicited SAEs related to virus challenge from Day 0 up to planned discharge from quarantine (Day 8, am).<br>• Use of concomitant medications from Day 0 up to the Day 28 (±3 days) follow-up visit. |
| | **Tertiary / Exploratory*:** | To explore Neumifil concentrations in blood (single and multiple doses). | Neumifil concentrations will be explored in blood. |
| | | To evaluate antibody (immunoglobulin [Ig] A [IgA] and G [IgG]) development in Neumifil-treated participants (single and multiple doses), compared to placebo. | Development of antibodies (IgA, IgG) against the virus will be evaluated in serum samples. |

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| | To evaluate antibody (IgA and IgG) response to the virus. | Anti-drug antibody (ADA) (IgA, IgG) development will be evaluated in serum samples. |
| | To evaluate cytokine and chemokine responses in nasal samples in Neumifil-treated participants (single and multiple doses), compared to placebo. | Cytokines and chemokines will be assayed in nasal samples. |
| * Note that tertiary/exploratory objectives and endpoints are optional and might be assessed only if needed; therefore, not all testing might be performed and reported. | | |

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| Hypothesis | The primary statistical hypothesis is that prophylactic treatment with Neumifil will significantly reduce the incidence and/or the severity of symptomatic influenza infection after influenza viral challenge when compared to placebo. |
| Investigational medicinal product (IMP) | • Neumifil, liquid for intranasal spray administration (active)<br>• Liquid for intranasal spray administration (placebo) |
| Challenge agent | Influenza A/Perth/16/2009 (H3N2) virus |
| Challenge agent route | Intranasally, [redacted] |
| Challenge agent titre | ~$10^{5.5}$ tissue culture infective dose (50%) ($TCID_{50}$) |
| Study population | Healthy adult male or female participants aged between 18 and 55 years old, inclusive, with a total body weight ≥50 kg and body mass index (BMI) ≥18 kg/$m^2$ and ≤35kg/$m^2$, who have been determined to be serosuitable with regard to pre-existing antibody levels to the influenza challenge virus. |
| Summary of study design | This is a single-centre, randomised, double-blind, placebo-controlled, proof-of-concept Phase 2 study in healthy adult male or female participants aged between 18 and 55 years old, inclusive. The primary goal of this Phase 2 study is to assess the pre-exposure prophylactic antiviral activity against influenza, safety, and tolerability of Neumifil via a human viral challenge model.<br>Each participant will receive one of 3 treatments:<br>• Neumifil once daily for 3 days on Days -3 to -1 (multiple dose active treatment).<br>• A single dose of Neumifil on Day -3 and placebo once daily on Days -2 and -1 (single dose active treatment).<br>• Placebo once daily for 3 days on Days -3 to -1. |

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| | A total of up to 100 evaluable participants is planned to be enrolled in this study: 30 participants on multiple dose active treatment, 30 participants on single dose active treatment, and 40 participants on placebo.<br><br>The study is divided into the following phases:<br><br>**Screening phase:**<br><br>From Day -93 to Day -5 (prior to quarantine admission). Historical generic screening data collected through the hVIVO generic screening process may be transferred to this study after the study-specific consent form has been signed by the participant.<br><br>**Inpatient phase:**<br><br>Participants will be resident in the quarantine unit for approximately 13 days (from Day -4 to Day 8). Procedures will include:<br>• **Pre-human viral challenge:**<br>○ Admission to quarantine unit on Day -4.<br>○ Baseline assessments and randomisation will be conducted as per Schedule of Events (SoE) up to Day -3, predose.<br>○ Administration of Neumifil and/or placebo once daily on Days -3 to -1, according to randomisation.<br>• **Human viral challenge:**<br>○ Influenza virus inoculation on Day 0.<br>• **Post-human viral challenge:**<br>○ Day 1 onwards and each day – study assessments will be conducted as per SoE.<br>○ Discharge from the quarantine unit on Day 8 (participants may remain longer, at the principal investigator's [PI's] discretion, if they are still shedding the influenza A/Perth/16/2009 (H3N2) virus challenge strain or have symptoms of influenza).<br><br>**Outpatient phase:**<br>• Final follow-up visit: Day 28 (±3 days).<br><br>Study assessments will be conducted as per SoE. |
| Randomisation | 3:3:4 to Neumifil multiple dose active treatment, Neumifil single dose active treatment, or placebo |
| Participant replacement strategy | Participants may be replaced in this study.<br>[redacted] |

<table>
<tr><td></td><td>[redacted]</td></tr>
<tr><td>Expected duration of participation per participant</td><td>Approximately 4 months from screening to the participant's last scheduled visit.</td></tr>
<tr><td>Overall duration of clinical phase</td><td>The length of the clinical phase is expected to be approximately 7 months from the first participants planned first study visit (screening visit) to the last participants last scheduled study visit.</td></tr>
<tr><td>End of study</td><td>The end of the study is defined as the date of the last visit of the last participant in the study.</td></tr>
<tr><td>Sample size determination</td><td>The number of 40 participants in the placebo arm and 60 (30 in each dose arm) in the pooled Neumifil group selected for this study will provide a power of at least 80% to detect a significant reduction in the primary endpoints:<ul><li>of 70% compared to the placebo arm in symptomatic influenza infection rate, assuming a symptomatic infection rate of 27.8% in the placebo arm,</li><li>of 65% compared to the placebo arm in peak TSS, assuming a coefficient of variation (CV) of 125%,</li></ul>using a 1-sided 0.05 type-one error rate for each of the 2 comparisons, without adjustment for multiple testing.<br><br>The table below summarises the power achieved with 40 versus 60 participants (for the placebo and pooled active treatment arms, respectively) for the 2 primary endpoints and some secondary endpoints.<br><br>
<table>
<tr><th>Endpoint</th><th>Assumption (placebo arm)</th><th>Relative reduction</th><th>Power (*)</th></tr>
<tr><td>Symptomatic infection rate</td><td>rate=27.8%</td><td>70%</td><td>81.5%</td></tr>
<tr><td>Peak TSS</td><td>CV=125%</td><td>65%</td><td>81.2%</td></tr>
<tr><td>VL-AUC</td><td>CV=91%</td><td>50%</td><td>84.8%</td></tr>
<tr><td>VLPEAK</td><td>CV=63.5</td><td>40%</td><td>92.2%</td></tr>
<tr><td>TSS-AUC</td><td>CV=155%</td><td>80%</td><td>80.7%</td></tr>
</table>
(*) Power achieved with placebo and 60 Neumifil participants (alpha 0.05 1-sided).<br>CV = coefficient of variation.</td></tr>
</table>

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| Statistics | **Primary Efficacy Analysis**<br><br>The primary efficacy analysis will be conducted on the per protocol (PP) analysis set.<br><br>The PP analysis set will consist of all participants randomised, having received the planned dose of IMP (Neumifil 3 doses on Days -3 to -1, or 1 single dose of Neumifil on Day -3 followed by 2 doses of placebo on Days -2 and -1, or placebo 3 doses on Days -3 to -1, according to randomisation) and challenged with the study virus, who complete the quarantine period up to its planned final day (Day 8) and present no major deviation likely to impact the evaluation of the primary efficacy endpoint.<br><br>For the symptomatic infection rate, the estimator with its 2-sided 90% and 95% confidence intervals (CIs) will be presented by treatment arm. The differences between the pooled active treatment arms and the placebo arm, and between each active treatment dose arm and the placebo arm, will be computed with their 2-sided 90% and 95% CIs. The 3 pairwise comparisons will use the Pearson Chi-square test, or the Fisher exact test if the assumptions for the Chi-square test are not met. Each test will use a nominal 1-sided type-one error of 0.05 without adjustment for multiplicity. In addition, the difference between the 2 Neumifil dose arms will be computed with its 90% and 95% CIs but no formal statistical test will be computed.<br><br>For the peak TSS, the mean and median and the 2-sided 90% and 95% CIs for the mean will be presented by treatment arm. The differences between the pooled active treatment arms and the placebo arm, and between each active treatment dose arm and the placebo arm, will be computed with their 2-sided 90% and 95% CIs. The 3 pairwise comparisons will use the Wilcoxon rank-sum test. Each test will use a nominal 1-sided type-one error of 0.05 without adjustment for multiplicity. In addition, the difference between the 2 Neumifil dose arms will be computed with its 90% and 95% CIs but no formal statistical test will be computed.<br><br>Further details on the primary efficacy analysis, secondary efficacy analyses, and safety analyses will be provided in the SAP. |

## 1.1. Study Schematic: On-study Participant Progression

| SCREENING PHASE | INPATIENT PHASE: QUARANTINE/ISOLATION, DOSING, AND HUMAN VIRAL CHALLENGE | | | | OUTPATIENT PHASE |
|---|---|---|---|---|---|
| Day -93 to Day -5<br>Screening* | Day -4<br>Admission to quarantine unit | Day -3 to Day -1<br>Dosing with Neumifil and/or placebo | Day 0<br>Inoculation with challenge virus (influenza) | Day 8<br>Discharge from quarantine unit** | Day 28 (±3 days)<br>Follow-up visit/final contact |

[redacted]

[redacted]

[redacted]

## 1.2. Schedule of Events

| Study Phase ➔ | Screening Phase* | Inpatient Phase (Quarantine Isolation and Human Viral Challenge) | | | | | | | | | | | | | | Outpatient Phase | Early Withdrawal Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Admission to Quarantine | Dosing with Neumifil/Placebo | | | Human Viral Challenge (HVC) | | | Post Human Viral Challenge | | | | | | | Dis-charge | Follow-up Clinic Visit | |
| Study Day # ➔ | Day -93 to Day -5 | Day -4 | Day -3 | Day -2 | Day -1 | Day 0 | | | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 28 (±3 days) | Quarantine post Challenge |
| Procedure ➔ | | | | | | Pre-HVC | HVC | Post HVC | | | | | | | | | | |
| Written consent (a) | X | [redacted] | | | | | | | | | | | | | | | | |
| Eligibility criteria (+) | X | | | | | | | | | | | | | | | | | |
| Suitability for human viral challenge | | | | | | | | | | | | | | | | | | |
| Medical & medication history | X | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | |
| Height & weight, body mass index (BMI) (b) | X | | | | | | | | | | | | | | | | | |
| Patient Health Questionnaire-9 (PHQ-9) | (X) | | | | | | | | | | | | | | | | | |
| Generalised Anxiety Disorder Questionnaire-7 (GAD-7) | (X) | | | | | | | | | | | | | | | | | |
| Alcohol breath test | X | | | | | | | | | | | | | | | | | |
| Urinalysis | X | | | | | | | | | | | | | | | | | |
| Urine drugs of misuse and nicotine screen | X | | | | | | | | | | | | | | | | | |
| Urine pregnancy test (female participants of childbearing potential) | X | | | | | | | | | | | | | | | | | |
| Complete physical examination | X | | | | | | | | | | | | | | | | | |
| Symptom-directed physical examination (incl. nasal) | | | (X) | (X) | (X) | (X) | | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | | | |

| Study Phase ➔ | Screening Phase* | Inpatient Phase (Quarantine Isolation and Human Viral Challenge) | | | | | | | | | | | | | | Outpatient Phase | Early Withdrawal Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Admission to Quarantine | Dosing with Neumifil/Placebo | | | Human Viral Challenge (HVC) | | | Post Human Viral Challenge | | | | | | Dis-charge | Follow-up Clinic Visit | |
| Study Day # ➔ | Day -93 to Day -5 | Day -4 | Day -3 | Day -2 | Day -1 | Day 0 | | | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 28 (±3 days) | Quarantine post Challenge |
| Procedure ➔ | | | | | | Pre-HVC | HVC | Post HVC | | | | | | | | | | |
| Vital signs (heart rate, respiratory rate, systolic blood pressure [SBP], diastolic blood pressure [DBP], peripheral arterial oxygen saturation [$SpO_2$]) (c) | X | [redacted] | | | | | | | | | | | | | | | | |
| Tympanic temperature (c) | X | | | | | | | | | | | | | | | | | |
| Symptom diary card | | | | | 3X | 3X | | | 3X | 3X | 3X | 3X | 3X | 3X | 3X | X | | |
| Solicited IMP self-assessment diary card | | | 2X | 2X | 2X | | | | | | | | | | | | | |
| 24-hour tissue count & nasal discharge weight (d) | | | | | X | X | | | X | X | X | X | X | X | X | X | | (X) |
| Spirometry (e) | X | [redacted] | | | | | | | | | | | | | | | | |
| 12-lead electrocardiogram (ECG) (f) | X | | | | | | | | | | | | | | | | | |
| **Product Administration** | | | | | | | | | | | | | | | | | | |
| Randomisation (g) | | | X | | | | | | | | | | | | | | | |
| Investigational medicinal product (IMP; Neumfil/placebo) dosing | | | X | X | X | | | | | | | | | | | | | |
| Challenge virus inoculation | | | | | | | X | | | | | | | | | | | |

| Study Phase ➔ | Screening Phase* | Inpatient Phase (Quarantine Isolation and Human Viral Challenge) | | | | | | | | | | | | | | Outpatient Phase | Early Withdrawal Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Admission to Quarantine | Dosing with Neumifil/Placebo | | | Human Viral Challenge (HVC) | | | Post Human Viral Challenge | | | | | | | Dis-charge | Follow-up Clinic Visit | |
| Study Day # ➔ | Day -93 to Day -5 | Day -4 | Day -3 | Day -2 | Day -1 | Day 0 | | | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 28 (±3 days) | Quarantine post Challenge |
| Procedure ➔ | | | | | | Pre-HVC | HVC | Post HVC | | | | | | | | | | |
| **Collection of Blood Samples** | | | | | | | | | | | | | | | | | | |
| Serum follicle-stimulating hormone (FSH) (postmenopausal female participants) | [redacted] | | | | | | | | | | | | | | | | | |
| Serum β-human chorionic gonadotrophin (β-HCG) pregnancy test (all female participants) | | | | | | | | | | | | | | | | | | |
| Human immunodeficiency virus (HIV) & hepatitis B, C serology | | | | | | | | | | | | | | | | | | |
| Haematology (h) | | | | | | | | | | | | | | | | | | |
| Biochemistry (h) | | | | | | | | | | | | | | | | | | |
| Coagulation | | | | | | | | | | | | | | | | | | |
| Thyroid function test | | | | | | | | | | | | | | | | | | |
| Blood – serum humoral immunity to virus | X | X | | | | | | | | | | | | | | | X | (X) |
| Blood –anti-drug antibody (ADA) (immunoglobulin [Ig] A [IgA] and G [IgG]) | | X | | | | | | | | | | | | | | | X | (X) |
| Blood – PAXgene ribonucleic acid (RNA) | | X | | | X | | | | | | X | | | | X | | X | |
| Blood – bioanalysis (i) | | | X | X | X | | | | | | | | | | | | | |
| **Collection of Respiratory Samples** | | | | | | | | | | | | | | | | | | |
| Nasopharyngeal swab – respiratory pathogen screen including severe acute | | X | | | | | | | | | | | | | | | | |

| Study Phase ➔ | Screening Phase* | Inpatient Phase (Quarantine Isolation and Human Viral Challenge) | | | | | | | | | | | | | | Outpatient Phase | Early Withdrawal Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Admission to Quarantine | Dosing with Neumifil/Placebo | | | Human Viral Challenge (HVC) | | | Post Human Viral Challenge | | | | | | | Dis-charge | Follow-up Clinic Visit | |
| Study Day # ➔ | Day -93 to Day -5 | Day -4 | Day -3 | Day -2 | Day -1 | Day 0 | | | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 28 (±3 days) | Quarantine post Challenge |
| Procedure ➔ | | | | | | Pre-HVC | HVC | Post HVC | | | | | | | | | | |
| respiratory syndrome coronavirus 2 (SARS-CoV2) (e.g., Biofire) (j) | | | | | | | | | | | | | | | | | | |
| Nasopharyngeal swab – viral discharge test | | | | | | | | | | | | | | | (X) | (X) | | |
| Nasopharyngeal swab – virology and exploratory purposes (k) | | | | | | | | | X | BD | BD | BD | BD | BD | BD | X | | |
| Nasosorption – inflammatory markers (e.g., cytokines/chemokines) and other protein biomarkers (l) | | | X | | | X | | | X | | | | | | | X | X | |
| **Safety Assessments** | | | | | | | | | | | | | | | | | | |
| Adverse event (AE) recording (m) | | Continuous | | | | | | | | | | | | | | | | |
| Concomitant medications (m) | | Continuous | | | | | | | | | | | | | | | | |

## KEY NOTES FOR TIME AND EVENTS SCHEDULE

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# 2. Introduction

Neumifil™ is a first-in-class carbohydrate binding module (CBM) 40 and is being developed for the universal treatment of influenza virus, respiratory syncytial virus (RSV), human rhinovirus, and Coronavirus Disease 2019 (COVID19).

## 2.1. Background

### 2.1.1. Influenza

Influenza viruses are associated with significant human disease and cause annual epidemics during autumn and winter. Although most people recover within 1 to 2 weeks without requiring medical attention, seasonal influenza yearly results in approximately 3 to 5 million cases of severe illness and up to 500,000 deaths worldwide, particularly among the very young, elderly, and chronically ill. Influenza caused an estimated yearly average of 23,600 deaths between seasons 1976 and 2007 and more than 200,000 hospitalisations in the United States. Comparable mortality and morbidity rates have been reported for European countries. Currently, the influenza type A viruses H1N1 and H3N2 are circulating in humans, along with influenza type B viruses. H3N2 viruses have been predominant in most seasons and have caused a higher number of deaths and hospitalisations than H1N1 and influenza B viruses (Nunes et al, 2011; Thompson et al, 2004; Zucs et al, 2005).

The neuraminidase inhibitors zanamivir and oseltamivir are currently recommended for the treatment and/or (post-exposure) prophylaxis of influenza A and B virus infections (Weinstock and Zuccotti, 2009; Fiore et al, 2011). However, new drugs are now required as there have been reports of the emergence of resistance after oseltamivir treatment (Dharan et al, 2009; Poland et al, 2009; Stephenson et al, 2009), and the increasing use of zanamivir monotherapy may lead to the development of zanamivir resistance. Xocluza (baloxavir marboxil) was subsequently developed and is available in several countries for treatment and post-exposure prophylaxis for influenza A and B. However, there remains a need to develop better vaccines (demonstrating high efficacy, with longer or broader protection, or with faster manufacturing) as well as additional antivirals and immunomodulators to manage infection, transmission, and disease.

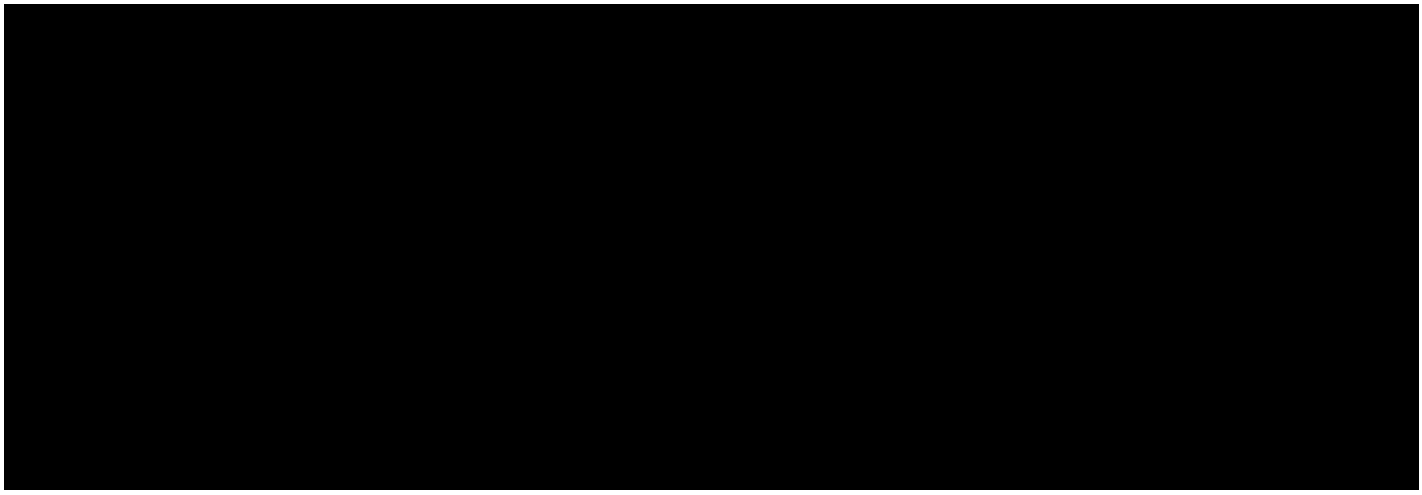
Progress towards a medicinal agent that provides protection against a broad range of influenza strains with a longer duration of protection, otherwise known as a “universal vaccine”, has been disappointing. The monoclonal antibody therapeutics developed to date have suffered from limited spectrum and commercial limitations due to high dosing requirements and/or the need for multiple antibody cocktails to achieve a desired spectrum and efficacy. Thus, a significant unmet need exists for long-acting universal protective agents.

The influenza human challenge model was established to not only aid understanding of influenza disease and transmission, but to also assess the efficacy of antivirals, immunomodulators, and vaccines (as reviewed by Lambkin-Williams et al, 2018; Yogaratnam et al, 2019; Bueno de Mesquita et al, 2021; Nguyen-Van-Tam et al, 2020; Ramos-Sevillano et al, 2019). hVIVO has given different influenza strains to over 1,300 volunteers over the last 20 years. The influenza A/Perth/16/2009 (H3N2) virus challenge strain used in the majority of studies to date has been given to over 400 volunteers by hVIVO. The virus has been well tolerated with no virus-related serious adverse events (SAEs) occurring in any of the participants inoculated to date. Furthermore, the challenge virus has been shown to induce measurable disease profiles with clear

distinction from non-infected participants and study participants have approximately 60% to 75% chance of becoming infected following the administration of the virus. Typical influenza illness is characterised by an abrupt onset of rhinitis, nasal stuffiness, fever, malaise, myalgia (muscle aches), and sore throat. In healthy adults, the illness usually resolves without any treatment, with relief of symptoms occurring naturally within 3 to 5 days. The disease profiles of the challenge agent are consistent with the mild to moderate disease profiles expected with wild-type challenge viruses in healthy adult participants. In summary, the influenza A/Perth/16/2009 (H3N2) challenge virus is considered safe, well tolerated, and induces appropriate disease pathogenesis to be an effective viral challenge agent in the human viral challenge studies.

### 2.1.2. Neumifil

[redacted]



CBM = carbohydrate binding module; TD = trimerisation domain.

**Figure 1-2: Modifications made in the construction of HEX17 from parent CBM Sp2CBMTD**

## 2.1.2.1. Nonclinical Studies

### *2.1.2.1.1. In Vitro And In Vivo Pharmacology*

[redacted]

### *2.1.2.1.2. Safety Pharmacology*

A functional observation battery was used to assess neurotoxicity of Neumifil in a 28-day study in rats. No neurotoxicity was observed after repeated doses up to 1,040 µg/animal/day, although a slight increase in the presence of pinna reflex was seen in both male and female treated animals. In a functional observation battery in primates Neumifil had no significant central nervous system effects at repeated doses up to 1.65 mg/kg/day for 28 days.

Cardiovascular safety of Neumifil was tested in a 28-day repeat dose study in Cynomolgus monkeys. Animals received repeated doses up to 1.25 mg/kg/day, and there were no changes in electrocardiogram (ECG), or in diastolic and systolic blood pressure (SBP, DBP).

The pharmacology of Neumifil does not suggest any respiratory risk, and no significant lung pathology has been noted in efficacy studies in mice and rats, or in dose-finding studies. Specific respiratory observations were made during the 28-day repeat dose study in primates. There were no changes in respiratory signs (rhinorrhoea, sneezing, coughing, abnormal breath sounds, respiratory rate, and breathing depth).

#### *2.1.2.1.3. Pharmacokinetics*

The absorption and pharmacokinetics (PK) of Neumifil have been studied after single intravenous and intranasal doses in rats. Neumifil 0.5 mg/kg given intravenously yielded a mean maximum observed concentration ($C_{max}$) of 1,240 ng/mL, area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) of 2,360 ng.h/mL, and a terminal half-life ($t_{1/2}$) 24.1 hours (range 9.29–46.0 hours). Pharmacokinetic parameters could not be calculated after intranasal administration of 4 mg/kg Neumifil, because plasma concentrations were above lower limit of quantification (LLOQ: 25.0 ng/mL) in only a single sample at 2 hours postdose (plasma concentration 42.8 ng/mL). Bioavailability of intranasal Neumifil was therefore considered to be <5%.

Very low plasma concentrations of Neumifil were detected during the 28-day repeated dose study in rats. The paucity of samples with quantifiable concentrations of Neumifil precluded any calculation of PK parameters, but systemic exposure was clearly minimal after repeated intranasal administration of doses up to 1,040 µg/day. Given the low plasma concentrations of Neumifil after intranasal dosing, its distribution has not been studied.

It is anticipated that intranasal Neumifil (a protein) will be broken down in the nasal mucosa by local peptidases to yield oligopeptides and free amino acids. Thus, further investigation of Neumifil metabolism is deemed unnecessary.

#### *2.1.2.1.4. Toxicology*

In the rat dose-range finding study, rats received intranasal doses up to 1,000 µg/day for 7 days, and there were no treatment-related deaths or significant clinical observations. However, some female rats had a slight decrease in body weight gain (average 3%), attributed to decreased food consumption. The maximum tolerated dose was 1000 µg/animal/day.

In the pivotal Good Laboratory Practice (GLP) 28-day repeated dose toxicity study in rats, animals received intranasal doses of 520, 780, and 1,040 µg/animal/day, but few samples had plasma Neumifil concentrations above LLOQ. The following PK parameters were estimated for Day 28: $C_{max}$ 123 ng/mL; time to maximum concentration ($t_{max}$) 2 hours; and $AUC_{0-\infty}$ 381 ng.h/mL. No animal died, but significant weight loss occurred at the 2 highest dose levels (6% in males and 7% in females). That adverse effect was reversible after 2 weeks of recovery. Abnormal respiratory sounds (loud breathing and/or respiratory crackles) were observed at all dose levels but remitted after dosing was stopped. Mild to moderate inflammatory and reactive changes in the nasal mucosa, associated with polymorphonuclear cell infiltration and goblet cell proliferation, were found in all treatment groups but were considered adverse only the at the mid and top dose levels. Inflammatory changes were noted also in respiratory tissues (larynx, trachea, bronchi, and bronchioles) at the 2 highest dose levels of Neumifil, but animals recovered fully after 2 weeks. The no observed adverse effect level (NOAEL) in rats after 4 weeks of dosing was 2.5 mg/kg/day.

In a non-GLP dose-range finding study, Cynomolgus monkeys received doses up to 1.25 mg/kg/day for 7 days. There were no treatment-related deaths or significant clinical findings.

Doses of 0.8, 1.20 and 1.65 mg/kg/day were tested in a GLP 28-day repeated dose Cynomolgus monkey toxicity study. All plasma concentrations of Neumifil were below LLOQ. There were no deaths and no effects related to the test item. Anti-drug antibody (ADA) analysis showed weak seroconversion in 4 animals, but ADA titres were similar to those in untreated animals so Neumifil was of low immunogenicity. The NOAEL in Cynomolgus monkeys after 28 days of dosing was 1.65 mg/kg/day.

#### *2.1.2.1.5. Pharmacodynamics*

Doses of up to 100 µg *Sp*2CBMTD were administered to BALB/c mice to investigate the potential mechanism of action of the parent family of HEX17, and its efficacy in preventing and treating infection with the influenza virus. *Sp*2CBMTD was either administered prophylactically to mice that were then challenged with a lethal dose of the virus or administered after the viral challenge. As well as promoting animal survival (80–100% when administered prophylactically, or 40% after exposure to the virus), cytokine analysis revealed that *Sp*2CBMTD stimulated a proinflammatory response when given as a prophylactic. [redacted]

### 2.1.2.2. Clinical Studies

A first-in-human, single ascending and multiple ascending dose study has been conducted, is clinically complete, but has not yet been fully analysed. [redacted] No SAEs and no deaths occurred. In the single dose groups adverse events (AEs) were related to short-lived nasal irritation, desire to sneeze, unpleasant taste, and changes in taste and smell. In the multiple dose groups, the participants reported the same effects on nasal irritation and desire to sneeze. Change in taste and smell lasted for up to 4 days.

Two participants reported short-lived nose bleeds sometime after administration of study intervention and these short-lived events were not considered related to the study intervention but could be related to the instrumentation of the nose.

One participant experienced a fall in forced expiratory volume in 1 second ($FEV_1$) and forced vital capacity (FVC) 8 hours after the first dose, spirometry was normal at 4 hours postdose and had returned to baseline at 12 hours postdose. The participant met the protocol criteria for withdrawal from the study and was withdrawn. The participant was asymptomatic throughout the event. The timing of changes in spirometry are temporally related to the administration of study intervention but are of an unusual time-course for an effect of the study intervention on respiratory function. This one-off event is not considered a reason to stop development.

Overall Neumifil was well tolerated in the healthy population under study, when administered as single or multiple (up to 7) doses and further investigation is warranted.

In summary, Neumifil is a novel candidate for the pre-exposure prophylaxis of viral respiratory tract infections. Neumifil has low to minimal risk of generating viral resistance because of its host- and viral-targeting modes of action. Neumifil's *in vitro* and *in vivo* animal data, clinical data, potential pan-viral efficacy, and toxicology profile makes it suitable for progression to a viral challenge study.

## 2.2. Study Rationale

The purpose of this Phase 2 study is to assess the efficacy, safety, and tolerability of a multiple dosing regimen (once daily for 3 days) and of a single dose of intranasal Neumifil, administered to healthy adults, initiated prior to being challenged with the influenza A/Perth/16/2009 (H3N2) virus. The main comparison will be between both dosing regimens pooled and the placebo arm. The comparison of each dose arm to

the placebo arm is not expected to elicit statistically significant difference, but will provide estimates of the relative efficacy of the 2 dosing regimens.

The anticipated use of Neumifil is to prevent viral infection in patients with underlying pulmonary disease (e.g., chronic obstructive pulmonary disease, bronchiectasis), in whom viral infections induce exacerbations of the underlying pulmonary disease. Neumifil will be administered on a regular basis (daily or possibly weekly) to prevent viral respiratory infections.

Influenza challenge strains have been used for over 20 years by both hVIVO and others and have helped assess numerous antiviral, immunomodulating, and vaccine therapies. Specifically, hVIVO has safely and successfully used the influenza A/Perth/16/2009 (H3N2) virus challenge strain in over 400 healthy participants (18 to 64 years of age).

## 2.3. Benefit/Risk Assessment

### 2.3.1. Risk Assessment

The known risks to participants are detailed in Table 2-1. However, there may also be risks that are unforeseen and unanticipated (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 staff and appropriate facilities will be available to provide medical emergency care.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of Neumifil be found in the Investigator's Brochure.

**Table 2-1: Risk Assessment**

| Potential Risk of Clinical Significance | Description of Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention** | | |
| Intranasal dosing with Neumifil | Available safety data shows Neumifil to have an acceptable safety profile as described in Section 2.1.2, Neumifil. Signs and symptoms observed after dosing with Neumifil in the first-in-human study include nasal irritation, desire to sneeze, unpleasant taste and changes in taste and smell, nasal discomfort, product after-taste, sneezing, nasal dryness, nasal congestion, rhinorrhoea, rhinalgia, throat irritation, hypoesthesia oral, parosmia. | If observed, the potential reactions will be monitored. In general, these short-term reactions do not require treatment.<br>The protocol schedule and assessments allow for adequate and continuous monitoring of safety parameters. |
| Intranasal dosing with placebo | The placebo contains excipients which may elicit effects. | If observed, the potential reactions will be monitored. In general, these short-term reactions do not require treatment.<br>The protocol schedule and assessments allow for adequate and continuous monitoring of safety parameters. |
| **Study procedures** | | |
| Blood sampling | Pain or bruising at the site where blood is drawn. | Blood samples will be obtained by a trained professional. |
| | Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle insertion. | Blood samples will be obtained by a trained professional and procedures will be put in place to avoid injury from fainting. |
| | There is a possibility that in the process of collecting blood a nerve may be injured. | Procedure to be performed by qualified personnel. |
| | Blood tests performed to address the health of the participants at screening and during the study may indicate that a participant has an infection that he/she was not previously aware of (such as 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. |

| Potential Risk of Clinical Significance | Description of Risk | Mitigation Strategy |
|---|---|---|
| Nasal sampling | Collection of respiratory (nasal) samples 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 |
| **Influenza A/Perth/16/2009 (H3N2) virus infection from inoculation** | | |
| influenza A/Perth/16/2009 (H3N2) virus infection & severe complications | Approximately 60% to 75% chance of becoming infected with influenza (influenza A/Perth/16/2009 [H3N2] virus). Typical influenza illness: abrupt onset of rhinitis, nasal stuffiness, fever, malaise, myalgia (muscle aches), and sore throat.<br>Severe complications are not expected as these tend to occur almost exclusively in infants, elderly, and persons of any age with chronic comorbidities and significant immune compromise and not in healthy adults with no comorbidities of coinfections. | The safety profile of the influenza A/Perth/16/2009 (H3N2) virus is well characterised in healthy adults as this has been used for over 20 years by hVIVO. At hVIVO more than 400 healthy participants aged 18 to 64 years have been challenged with influenza A/Perth/16/2009 (H3N2) virus.<br>Influenza infection in healthy adults usually resolves without any treatment, with relief of symptoms occurring naturally within 3 to 5 days.<br>Strict inclusion and exclusion criteria will apply to ensure only healthy adults are enrolled in this study.<br>There will be a daily medical monitoring in a quarantine unit for at least 8 days post-human viral challenge.<br>Qualified medical and nursing staff in the quarantine unit will monitor for and manage any symptoms. |
| Transmission of influenza A/Perth/16/2009 (H3N2) virus to participants' close contacts | Influenza A/Perth/16/2009 (H3N2) virus presence in nasal secretions can cause infection in close contacts. | The duration of the quarantine has been designed to allow for resolution of infectious virus (culturable) before discharge. This is based on experience to date with more than 400 inoculations. As appropriate, the PI/delegate may request additional testing of nasal swab samples using a qualitative virus antigen test to assist in determining participants' suitability for departure.<br>As an additional precaution, participants will be instructed to avoid close contact with vulnerable individuals as described in Section 2.3.1.1, Vulnerable Persons, for 2 weeks after they leave the quarantine unit. |

| Potential Risk of Clinical Significance | Description of Risk | Mitigation Strategy |
|---|---|---|
| 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.<br>In case the participants develop any cold sore, herpes or shingles; they may be treated symptomatically while at the quarantine unit. If it continues, they will be followed up until resolved or, if necessary, dependent on medical history, will be referred to their GP or any specific department at hospital, as required. |

Consult the Investigator's Brochure for detailed information on Neumfil.

#### 2.3.1.1. Vulnerable Persons

For the purposes of possible contact after leaving the quarantine unit, the participant should avoid close contact with vulnerable individuals for 2 weeks after they leave the quarantine unit. A vulnerable individual is a person 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:
  - [redacted]

#### 2.3.1.2. Risk Associated with Coronavirus Disease 2019 Pandemic

hVIVO has 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 Agent Inoculation:**

[redacted]

**Risk of Increased Severity of COVID-19 Infection After Study Intervention Administration:**

[redacted]

### 2.3.2. Benefit Assessment

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

Participants may develop some immunity to influenza A/Perth/16/2009 (H3N2) 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

Considering the measures taken to minimise risk to participants in this study, the potential risks identified in association with Neumifil treatment and influenza A/Perth/16/2009 (H3N2) virus infection are justified by the anticipated benefits linked to the evaluation of the antiviral activity of Neumifil in the viral challenge model which will contribute to the development of a new therapy for the prevention of seasonal and pandemic influenza.

# 3. Objectives and Endpoints

| | Objective(s) | Related Endpoints/Outcome Measure(s) |
|---|---|---|
| **Primary:** | *Efficacy* | |
| | To evaluate the effect of Neumifil in 1) reducing the incidence of symptomatic influenza infection and/or 2) reducing the severity of symptoms after influenza viral challenge, compared to placebo. | The study has 2 primary endpoints:<br>1) Reducing the incidence of symptomatic influenza infection:<br>• Reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed symptomatic influenza infection, defined as:<br>○ RT-PCR-confirmed influenza infection defined as 2 detectable (≥ lower limit of detection [LLOD]) RT-PCR measurements (reported on 2 or more independent nasal samples over 2 days), starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am),<br>AND<br>○ Any symptoms of grade ≥2 at a single time point.<br>2) Reducing the severity of symptoms:<br>• Peak symptoms diary card score: peak total symptoms score (TSS) as measured by graded symptom scoring system collected 3 times daily, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am). |
| **Secondary:** | *Efficacy* | |
| | To evaluate the effect of Neumifil in reducing clinical symptoms due to influenza viral challenge, compared to placebo. | • Area under the curve over time of total clinical symptoms score (TSS-AUC) as measured by graded symptom scoring system collected 3 times daily, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am).<br>• Peak daily symptom score: individual maximum daily sum of symptom score, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am).<br>• Number (%) of participants with grade 2 or higher symptoms, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am). |

| | Objective(s) | Related Endpoints/Outcome Measure(s) |
|---|---|---|
| | | • Duration of clinical symptoms: 1) any symptoms, 2) TSS of 2 or more (with at least 2 systems), and 3) grade 2 or higher symptoms, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am).<br>• Time to resolution from peak clinical symptoms as measured by graded symptom scoring system collected 3 times daily. Time to resolution is defined as the time (hours) from peak clinical symptoms until first time with TSS = 0 after which no further increase above 0 is observed. |
| | To evaluate the effect of Neumifil in reducing or shortening viral shedding after influenza viral challenge, compared to placebo. | • Area under the viral load-time curve (VL-AUC) of influenza challenge virus as determined by quantitative RT-PCR (qRT-PCR) on nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am).<br>• VL-AUC of influenza challenge virus as determined by tissue culture on nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am).<br>• Peak viral load (VLPEAK) of influenza as defined by the maximum viral load determined by qRT-PCR measurements in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am).<br>• VLPEAK as defined by the maximum viral load determined by quantitative viral culture measurements in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am).<br>• Duration of quantifiable influenza, assessed by qRT-PCR measurements in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am). Duration is defined as the time (hours) from first quantifiable until first confirmed unquantifiable assessment after their peak measure (after which no further virus is quantified).<br>• Duration of detectable influenza, assessed by qRT-PCR measurements in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am). Duration is defined as the time (hours) from first detectable until first confirmed undetectable |

| | Objective(s) | Related Endpoints/Outcome Measure(s) |
|---|---|---|
| | | assessment after their peak measure (after which no further virus is detected).<br>• Duration of quantifiable influenza viral culture measurements in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am). Duration is defined as the time (hours) from first quantifiable until first confirmed unquantifiable assessment after their peak measure (after which no further virus is quantified).<br>• Duration of detectable influenza viral culture measurements in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am). Duration is defined as the time (hours) from first detectable until first confirmed undetectable assessment after their peak measure (after which no further virus is detected).<br>• Time to resolution from VLPEAK as defined by the maximum viral load determined by qRT-PCR measurements in nasal samples. Time to resolution is defined as the time (hours) from VLPEAK until first confirmed undetectable assessment (after which no further virus is detected).<br>• Time to resolution from VLPEAK as defined by the maximum viral load determined by qRT-PCR measurements in nasal samples. Time to resolution is defined as the time (hours) from VLPEAK until first confirmed unquantifiable assessment (after which no further virus is quantified).<br>• Time to resolution from VLPEAK as defined by the maximum viral load determined by viral culture measurements in nasal samples. Time to resolution is defined as the time (hours) from VLPEAK until first confirmed undetectable assessment (after which no further virus is detected).<br>• Time to resolution from VLPEAK as defined by the maximum viral load determined by viral culture measurements in nasal samples. Time to resolution is defined as the time (hours) from VLPEAK until first confirmed unquantifiable assessment (after which no further virus is quantified). |

| | Objective(s) | Related Endpoints/Outcome Measure(s) |
|---|---|---|
| | To evaluate the effect of Neumifil in reducing nasal discharge, compared to placebo. | • Total weight of mucus produced, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am).<br>• Total number of tissues used by participants, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am). |
| | To evaluate the effect of Neumifil in reducing the incidence of influenza infection due to influenza viral challenge, compared to placebo. | • RT-PCR-confirmed influenza infection, defined as 2 quantifiable (≥ lower limit of quantification [LLOQ]) qRT-PCR measurements (reported on 2 or more independent nasal samples over 2 days), starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am).<br>• Occurrence of at least 1 positive quantitative (≥ LLOQ) cell culture measurement in nasal samples, starting from Day 1 (pm) up to planned discharge from quarantine (Day 8, am).<br>• Culture lab-confirmed symptomatic influenza infection, defined as:<br>○ Lab-confirmed culturable influenza infection (1 quantifiable [≥ LLOQ] cell culture measurement, starting from Day 1 [pm] up to planned discharge from quarantine [Day 8, am]),<br>AND<br>○ Any symptoms of grade ≥2 at a single time point.<br>Further sensitivity analysis may be performed on the above qRT-PCR-related endpoints where detection by qRT-PCR is reported above the LLOD instead of the LLOQ and/or using other definitions for the symptomatic component. Details will be provided in the statistical analysis plan (SAP).<br>• Number (%) of participants with lab-confirmed infection and fever (≥37.9°C). |
| | *Safety* | |
| | To evaluate the safety of intranasal doses of Neumifil, compared to placebo. | • Occurrence of AEs (solicited and unsolicited) up to the Day 28 (±3 days) follow-up visit, including any SAEs.<br>• Occurrence of unsolicited AEs of special interest (AESIs) up to the Day 28 (±3 days) follow-up visit. AESIs are: clinically significant reduction in $FEV_1$ and FVC. |

| | Objective(s) | Related Endpoints/Outcome Measure(s) |
|---|---|---|
| | To monitor the safety of the challenge virus. | • Occurrence of unsolicited AEs related to virus challenge from Day 0 up to planned discharge from quarantine (Day 8, am).<br>• Occurrence of unsolicited SAEs related to virus challenge from Day 0 up to planned discharge from quarantine (Day 8, am).<br>• Use of concomitant medications from Day 0 up to the Day 28 (±3 days) follow-up visit. |
| **Tertiary / Exploratory*:** | To explore Neumifil concentrations in blood (single and multiple doses). | Neumifil concentrations will be explored in blood. |
| | To evaluate antibody (immunoglobulin [Ig] A [IgA] and G [IgG]) development in Neumifil-treated participants (single and multiple doses), compared to placebo. | Development of antibodies (IgA, IgG) against the virus will be evaluated in serum samples. |
| | To evaluate antibody (IgA and IgG) response to the virus. | Anti-drug antibody (ADA) (IgA, IgG) development will be evaluated in serum samples. |
| | To evaluate cytokine and chemokine responses in nasal samples in Neumifil-treated participants (single and multiple doses), compared to placebo. | Cytokines and chemokines will be assayed in nasal samples. |
| * Note that tertiary/exploratory objectives and endpoints are optional and might be assessed only if needed; therefore, not all testing might be performed and reported. | | |

# 4. Study Design

## 4.1. Overall Design

This is a single-centre, randomised, double-blind, placebo-controlled, proof-of-concept Phase 2 study in healthy adult male or female participants aged between 18 and 55 years old, inclusive, utilising:

- Investigational medicinal product (IMP) (active): Neumifil, [redacted] once daily for 3 days on Days -3 to -1 (multiple dose active treatment) or [redacted] single dose on Day -3 (single dose active treatment), intranasally administered ([redacted] Neumifil [redacted]
- IMP (placebo): Matching placebo, once daily for 3 days on Days -3 to -1 (placebo treatment) or once daily for 2 days on Days -2 and -1 (single dose active treatment), intranasally administered [redacted]
- Challenge agent: influenza A/Perth/16/2009 (H3N2) virus challenge strain, ~$10^{5.5}$ tissue culture infective dose (50%) ($TCID_{50}$), intranasally administered.

The primary goal of this Phase 2 study is to assess the pre-exposure prophylactic antiviral activity against influenza, safety, and tolerability of Neumifil via a human viral challenge model.

Each participant will receive one of 3 treatments:

- Neumifil once daily for 3 days on Days -3 to -1 (multiple dose active treatment).
- A single dose of Neumifil on Day -3 and placebo once daily on Days -2 and -1 (single dose active treatment).
- Placebo once daily for 3 days on Days -3 to -1.

A total of up to evaluable 100 participants is planned to be enrolled in this study: 30 participants on multiple dose active treatment, 30 participants on single dose active treatment, and 40 participants on placebo.

The expected duration of study participation for a participant is 4 months, with the following sequence and duration of study phases:

- **Screening phase:** From Day -93 to Day -5 (prior to quarantine admission). Historical generic screening data collected through the hVIVO generic screening process may be transferred to this study after the study-specific consent form has been signed by the participant.
- **Inpatient phase:** Participants will be resident in the quarantine unit for approximately 13 days (from Day -4 to Day 8). Procedures will include:
    - **Pre-human viral challenge:**
        - Admission to quarantine unit on Day -4.
        - Baseline assessments and randomisation will be conducted as per Schedule of Events (SoE) up to Day -3, predose.
        - Administration of Neumifil and/or placebo once daily on Days -3 to -1, according to randomisation.
    - **Human viral challenge:**
        - Influenza virus inoculation on Day 0.

- **Post-human viral challenge:**
  - Day 1 onwards and each day – study assessments will be conducted as per SoE.
  - Discharge from the quarantine unit on Day 8 [redacted]

- **Outpatient phase:**
  - Final follow-up visit: Day 28 (±3 days).

Study assessments will be conducted as per SoE

The Study Schematic, showing participant progression through the study, is presented in Section 1.1, Study Schematic: On-study Participant Progression. The SoE is presented in Section 1.2, Schedule of Events.

## 4.2. Scientific Rationale for Study Design

The study will be conducted by hVIVO Services Limited, which has extensive experience with influenza challenge studies. Numerous studies have been performed using experimental influenza infection in human participants. To date, in hVIVO's studies, over 400 participants have been successfully and safely inoculated with influenza A/Perth/16/2009 (H3N2) virus. These studies demonstrated that adults could be infected by nasal inoculation and that experimental infection was safe. This influenza strain has been shown to cause symptoms and virus shedding that closely match natural infection.

Administration of IMP and challenge with influenza A/Perth/16/2009 (H3N2) virus will take place in hVIVO's specialised clinical facilities, in a quarantine unit. 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.

**Blinding, Control, and Randomisation**

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. It will allow a comparative evaluation of the efficacy of Neumifil.

Blinding will prevent the occurrence of conscious and unconscious bias in the conduct and interpretation of the study.

Randomisation will be used to prevent bias in the assignment of participants to treatment arms, to increase the likelihood that known and unknown participant characteristics (e.g., demographic and baseline characteristics) are equally balanced across treatment arms, and to enhance the validity of statistical comparisons across treatment arms.

## 4.3. Justification for Dose

All doses administered in the first-in-human study were well tolerated. In the multiple dose part of the study Neumifil was administered as a single daily dose of [redacted] Based on the safety profile and tolerability of Neumifil seen to date 3[redacted] would be appropriate.

An inoculum titre of approximately $10^{5.5}$ $TCID_{50}$ of the influenza A/Perth/16/2009 (H3N2) virus strain has been shown to cause disease profiles that are consistent with the mild to moderate disease profiles expected with wild-type challenge viruses in healthy adult participants.

## 4.4. Population to be Studied

Healthy adult participants.

## 4.5. Rationale for Trial Endpoints

The measures for evaluation of the safety and tolerability profile of Neumifil are standard for most clinical studies and follow the recommendations in the International Council for Harmonisation (ICH) guidelines.

The measures for evaluation of the pre-exposure prophylactic antiviral activity of Neumifil against influenza have been employed in previous studies conducted by hVIVO and are appropriate to characterise the efficacy of Neumifil, considering the Neumifil mode of action.

Biomarkers (cytokine and chemokine) and ADAs are exploratory in nature and do not have predefined endpoints.

## 4.6. 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 study visit or the last unscheduled study visit, as applicable. If a safety visit is required after the last scheduled study visit, this will be at the discretion of the PI/investigator as a duty of care, e.g., repeat spirometry or laboratory tests. These discretionary follow-up visits will not be considered part of the study 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 visit of the last participant in the study.

# 5. Study Population

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

## 5.1. Inclusion Criteria

| No. | **hVIVO APPROVED STANDARD INCLUSION CRITERIA**<br>**(Viral Challenge Volunteer Studies)**<br>Final v11.0, 08FEB2022 |
|---|---|
| To be eligible for the study, participants must meet all the following inclusion criteria: | |
| 1. | Written informed consent signed and dated by the participant and the investigator obtained before any assessment is performed. |
| 2. | Adult male or female aged between 18 and 55 years old, inclusive, on the day *prior* to signing the consent form. |
| 3. | A total body weight ≥50 kg and body mass index (BMI) ≥18 kg/m$^2$ and ≤35kg/m$^2$. |
| 4. | In good health with no history, or current evidence, of clinically significant medical conditions, [redacted]. |
| 5. | Participants will have a documented medical history either prior to entering the study or following medical history review with the study physician at screening. |
| 6. | The following criteria are applicable to female participants participating in the study.<br>a) Females of childbearing potential must have a negative pregnancy test prior to enrolment.<br>b) Females of non-childbearing potential:<br>a. Postmenopausal females defined [redacted]<br>b. Documented status as being surgically sterile [redacted] |
| 7. | The following criteria apply to female and male participants:<br>a) Female participants of childbearing potential must use 1 form of highly effective contraception. [redacted] |

| No. | **hVIVO APPROVED STANDARD INCLUSION CRITERIA**<br>**(Viral Challenge Volunteer Studies)**<br>Final v11.0, 08FEB2022 |
|---|---|
| | 1. [redacted]<br>b) Male participants must agree to the contraceptive requirements [redacted]<br>c) In addition to the contraceptive requirements above, male participants must agree not to donate sperm [redacted] |
| 8. | Serosuitable for the challenge virus<br>• The serology result obtained from the influenza antibody assay suggests that the participant is sensitive to influenza infection (i.e., likely to be infected following inoculation with the challenge virus; he/she must have no or low pre-existing serum levels of antibodies specific to the challenge agent). |

## 5.2. Exclusion Criteria

| NO | **hVIVO APPROVED STANDARD EXCLUSION CRITERIA**<br>**(Viral Challenge Volunteer Studies)**<br>Final v11.0, 08FEB2022 |
|---|---|
| Participants who meet any of the following exclusion criteria will not be included in the study. | |
| **Medical History** | |
| 1. | History of, or currently active, symptoms or signs suggestive of upper or lower respiratory tract (URT, LRT) infection within 4 weeks prior to the first study visit. |
| 2. | Any history or evidence of any clinically significant or currently active cardiovascular, respiratory, dermatological, gastrointestinal, endocrinological, haematological, hepatic, immunological (including immunosuppression), metabolic, urological, renal, neurological, or psychiatric disease and/or other major disease that, in the opinion of the investigator, may interfere with a participant completing the study and necessary investigations. [redacted]<br>[redacted]<br>e) [redacted] |
| 3. | Any participants who have smoked ≥10 pack years at any time (10 pack years is equivalent to 1 pack of 20 cigarettes a day for 10 years). |

| NO | **hVIVO APPROVED STANDARD EXCLUSION CRITERIA**<br>**(Viral Challenge Volunteer Studies)**<br>Final v11.0, 08FEB2022 |
|---|---|
| 4. | Females who:<br>a) Are breastfeeding, or<br>b) Have been pregnant [redacted]r<br>c) Have a positive pregnancy test at any point during screening or prior to first dosing with IMP. |
| 5. | a) Any history of anaphylaxis or history of severe allergic reactions [redacted] |
| 6. | Venous access deemed inadequate [redacted] |
| 7. | 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.<br>b) History of nasal polyps<br>c) Nasal inflammation present at screening on Day -4<br>d) 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.<br>e) Any nasal or sinus surgery within 3 months of the first study visit. |
| **Prior or Concomitant Medications and Assessments** | |
| 8. | a) Evidence of vaccinations within the 4 weeks prior to the planned date of first dosing with IMP.<br>b) Intention to receive any vaccination(s) before the last day of follow-up (with the exception of vaccinations recommended for COVID19 as defined by Medicines and Healthcare Regulatory Agency (MHRA)/government vaccination guidelines). No travel restrictions apply after the Day 28 (±3 days) follow-up visit.<br>c) Receipt of influenza vaccine (or another IMP relating to treatment of influenza) in the last 6 months prior to the planned date of viral challenge OR a diagnosis of influenza or influenza-like illness confirmed by a physician within the last 2 months prior to screening. |
| 9. | Receipt of blood or blood products, or loss (including blood donations) of 550 mL or more of blood during the 3 months prior to the planned date of first dosing with IMP or planned during the 3 months after the final follow-up visit. |
| 10. | a) Receipt of any investigational drug within 3 months (or 5 half-lives of the IMP used in the other study, whichever is greater), prior to the planned date of first dosing with IMP.<br>b) Receipt of 3 or more investigational drugs within the previous 12 months prior to the planned date of first dosing with IMP. |

| NO | **hVIVO APPROVED STANDARD EXCLUSION CRITERIA**<br>**(Viral Challenge Volunteer Studies)**<br>Final v11.0, 08FEB2022 |
|---|---|
| | c) Prior inoculation with a virus from the same virus-family as the challenge virus.<br>d) Prior participation in another human viral challenge study with a respiratory virus in the preceding 3 months, taken from the date of viral challenge in the previous study to the date of expected viral challenge in this study. |
| 11. | Use or anticipated use during the conduct of the study of concomitant medications (prescription and/or non-prescription), including vitamins or herbal and dietary supplements within the specified windows, unless in the opinion of the PI/investigator, the medication will not interfere with the study procedures or compromise participant safety. Specifically, the following are excluded:<br>a) Herbal supplements, any medication or product (prescription or over the counter) for symptoms of nasal congestion, or short or long-acting histamines, within 7 days prior to the planned date of first dosing with IMP.<br>b) Chronically used medications, vitamins, or dietary supplements, including any medications known to be moderate/potent inducers or inhibitors of cytochrome P450 (CYP) enzymes, within 21 days prior to the planned date of first dosing with IMP.<br>c) Over the counter medications (e.g., paracetamol or ibuprofen) where the dose taken over the preceding 7 days prior to the planned date of first dosing with IMP has exceeded the maximum permissible daily dose (e.g., ≥4 g paracetamol or ≥1.2 g ibuprofen over the preceding week).<br>d) Systemic (oral and parenteral) antiviral drugs, within 4 weeks prior to the planned date of first dosing with IMP.<br>e) Use of any intranasal medication, including saline douches, within the 30 days prior to admission. |
| 12. | a) Confirmed positive test for drugs of misuse and cotinine on first study visit. [redacted]<br>b) Recent 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 $FEV_1$ < [redacted]%, a FVC < [redacted], or an $FEV_1$/FVC ratio < [redacted] |
| 14. | Positive HIV, hepatitis B virus, or hepatitis C virus test. |
| 15. | Presence of fever [redacted] on Day -4 [redacted] |

| | |
|---|---|
| **NO** | **hVIVO APPROVED STANDARD EXCLUSION CRITERIA (Viral Challenge Volunteer Studies)** Final v11.0, 08FEB2022 |
| **Other** | |
| 16. | Those employed or immediate relatives of those employed at hVIVO or the sponsor. |
| 17. | 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

[redacted]

### 5.3.2. Caffeine, Alcohol, and Tobacco

[redacted]

### 5.3.3. Activity

Participants must refrain from strenuous exercise [redacted]

### 5.3.4. Other Restrictions

Participants will be instructed to avoid close contact with vulnerable people as described in Section 2.3.1.1, Vulnerable Population, for 2 weeks after they leave the quarantine unit.

## 5.4. Screen Failures

[redacted]

[redacted].

# 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 6-1.

## 6.1. Study Intervention(s) Administered

**Table 6-1: Study Interventions**

| **Intervention Name** | **Neumifil** | **Placebo** | **Influenza A/Perth/16/2009 (H3N2) Virus** |
|---|---|---|---|
| **Type** | Drug | Other | Virus |
| **Dose Formulation** | Liquid for intranasal spray administration | Liquid for intranasal spray administration | Capped vial, liquid for internasal drops administration |
| **Unit Dose Strength(s)** | [redacted] | Not applicable | The challenge agent titre is determined in an infectivity assay. The dose is approximately $10^{5.5}$ $TCID_{50}$ |
| **Dosage Level(s)** | <u>Multiple dose active treatment:</u> | | A single dose of challenge agent will be delivered |
| | 3-day once daily dosing regimen of [redacted] (Days -3 to -1), divided between left and right nostrils [redacted] | Not applicable | |
| | <u>Single dose active treatment:</u> | | |
| | [redacted] (Day -3) divided between left and right nostrils [redacted] | 2-day once daily dosing regimen of 0.28 mL (Days -2 and -1), divided between left and right nostrils [redacted] | |
| | <u>Placebo treatment:</u> | | |

| | | | |
|---|---|---|---|
| | Not applicable | 3-day once daily dosing regimen [redacted] (Days -3 to -1), [redacted] | |
| **Route of Administration** | Intranasal | Intranasal | Intranasal |
| **Use** | Experimental | Placebo | Infectious challenge agent |
| **Sourcing** | Provided by Pneumagen | Provided by Pneumagen | Provided centrally by hVIVO |
| **Packaging and Labelling** | The details of the packaging and labelling will be provided in the study-specific pharmacy manual | The details of the packaging and labelling will be provided in the study-specific pharmacy manual | Influenza challenge agent will be provided in vials. The details of the challenge agent provision will be provided in the analytical plan (AP) |
| **Current/Former Name(s) or Alias(es)** | Not applicable | Not applicable | Not applicable |

## 6.2. Preparation/Handling/Storage/Accountability

### 6.2.1. Investigational Product

Neumifil and placebo (IMP) will be supplied in prefilled nasal spray pump devices for intranasal administration. Details on dose preparation and administration are provided in the study-specific pharmacy manual.

hVIVO will receive supplies of IMP after the supply has received qualified person sign off by the Good Manufacturing Practice (GMP) sponsor's representative/pharmacy provider and has been released for shipment. All IMP supplies will be used only for this protocol and for no other purpose.

Ready-to-dispense IMP will be supplied at the beginning of the study. Once received at hVIVO, hVIVO study staff will perform stock level accountability and the IMP will be stored securely, according to the directions on the IMP labels. IMP accountability will be controlled by hVIVO and monitored by the study monitor throughout the study and at study close-out.

The PI/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 IMP is monitored. Accurate records will be

kept of when and how much IMP 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 IMP.

### 6.2.2. Challenge Agent

The challenge agent used in this study is influenza A/Perth/16/2009 (H3N2) virus.

The challenge agent stock was manufactured under current good manufacturing practices (cGMP). The challenge agent 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 agent is stored in a secure -80ºC freezer (normal temperature range -60°C to -90°C).

Each participant will be allocated a unique vial containing the challenge agent and will receive the inoculum intranasally. The inoculum will be prepared and/or provided according to the hVIVO Analytical Plan (AP) and administered in accordance with hVIVO standard operating procedure (SOPs).

All administrations will be made by a member of the study staff and witnessed by a second study staff member. The exact time of challenge agent inoculation will be recorded in the administration log. Accurate records will be kept of when and how much inoculum is prepared and/or provided and used. The oversight process will be signed off prior to administration of the challenge agent. Any noncompliance or problems with the inoculation will be recorded in the participant's source notes and reported to the PI/investigator.

[redacted].

### 6.2.3. All Study Interventions

The PI/investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorised investigator site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled area, and monitored (manual or automated) in accordance with the labelled storage conditions with access limited to the PI/investigator and authorised investigator site staff.

The PI/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)

Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

## 6.3. Randomisation and Blinding

[redacted] The randomisation number encodes the participant's assignment to one of 3 study arms (Neumifil multiple dose active treatment, Neumifil single dose active treatment, or placebo) in a 3:3:4 ratio.

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

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

Randomisation numbers will follow a 3-digit format e.g., [001]. If participants are replaced as per Section 7.4, Participant Replacement Strategy, the replacement participant will be 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 treatment as the participant who is being replaced.

A copy of the randomisation code list will be sent to the unblinded pharmacist preparing the IMP, so that IMP (Neumifil/placebo) can be prepared for each participant as appropriate. An independent statistician prepares the randomisation schedule, and the GMP pharmacy provider 's pharmacist/designee will prepare the participant level IMP doses in line with the randomisation schedule.

Each participant will be dispensed blinded IMP (Neumifil/placebo), labelled with his/her unique randomisation number, throughout the study. With the exception of the unblinded pharmacist, the unblinded statistician preparing the randomisation code list, and the quality assurance auditors where necessary, the PI/investigator and all other clinical and nonclinical 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.

Individual access to a secured Interactive Web Response System (IWRS) will be provided to the investigator. The website, compliant with 21CFR part 11 guidelines, will be used if unblinding is necessary. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. The blind should only be broken where knowledge of the IMP received is required to provide appropriate patient care. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. When the investigator breaks the code, he/she will have to indicate on the web site the reason of unblinding. The person who performed the unblinding and the date of time of code breaking will be automatically recorded. After confirmation the nature of treatment will appear on the screen. A notification with the nature of treatment will also be provided

by email. A notification, without the nature of treatment, will be provided to the study team. The investigator must notify the sponsor within 24 hours that the code has been broken.

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

Dosing with IMP must be discontinued after unblinding, but the participant will be followed up until resolution of any AEs.

## 6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention and challenge agent directly from the PI/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 electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the PI/investigator site staff other than the person administering the study intervention.

Any noncompliance 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 will be recorded in the source data from the time of the participant signing the study-specific ICF up to final study contact Day 28 (±3 days). Any medication (including over the counter or prescription medicines, vitamins, and/or herbal supplements) 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 PI/investigator and must notify the study staff as soon as possible if they are prescribed any medication. All medications must be stopped (with the exception as detailed in Table 6-3) prior to the planned date of first dosing with IMP unless in the opinion of the PI/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 6-2.

**Table 6-2: Prohibited Medication**

| Prohibited medication | Washout |
|---|---|
| Systemic (oral and parenteral) antiviral drugs. | [redacted] |
| Use or anticipated use during conduct of the study of concomitant medications (prescription and non-prescription), including vitamins or herbal and dietary supplements, unless in the opinion of the PI/investigator the medication will not interfere with | [redacted] |

| Prohibited medication | Washout |
|---|---|
| the study procedures or compromise participant safety. | [redacted] |
| Vaccines. | [redacted] |
| Any IMP used in another study. | [redacted] |

Any concomitant medication required for the participant's welfare may be given by the PI/investigator. However, it is the responsibility of the PI/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.

[redacted]

**Table 6-3: Permitted Medication**

| Permitted medication | Time period |
|---|---|
| Paracetamol | [redacted] |
| Ibuprofen | [redacted] |
| Oral contraceptives | Allowed at any time during the study. |
| [redacted]. | |

| Permitted medication | Time period |
|---|---|
| If, e.g., in an outbreak or pandemic, a newly instated national vaccination programme is applicable to an individual participant, the PI/investigator and sponsor will discuss on an individual basis if concomitant vaccination may be allowed, study dosing/viral challenge postponed, or the participant withdrawn from the study. | |

## 6.6. Dose Modification

This is not applicable in this study.

## 6.7. 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 PI/investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities possibly associated with overdose and the participant will be clinically followed up until any AE/SAE has resolved.
3. Obtain a plasma sample for measurement of plasma concentrations of Neumifil within 2 hours of the overdose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

The sponsor is responsible for notifying the MHRA and Research Ethics Committee (REC) of the potential serious breach within 7 days of becoming aware of it.

# 7. Discontinuation of Study Intervention/Withdrawal

## 7.1. Participant Withdrawal

[redacted]

## 7.2. Participant Discontinuation

[redacted]

Participants who are withdrawn from the study will be requested to attend an early withdrawal visit, with assessments as detailed in the SoE.

### 7.2.1. Temporary Discontinuation/Temporary Delay in Enrolment

[redacted]

## 7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he/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 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 the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the PI/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 are handled as part of Appendix 1, Regulatory, Ethical, and Study Oversight Considerations.

## 7.4. Participant Replacement Strategy

Participants may be replaced in this study.

[redacted].

## 7.5. Stopping Rules

The PI/investigator 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 serious adverse reactions (SUSARs) during the study and the procedures that should be performed in each case are presented in Table 7-1.

**Table 7-1: 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 the IMP will not take place. The PI/investigator and the SME will review the data and decide on whether it is appropriate to recommence IMP dosing (approval of a substantial amendment from the Competent Authorities is required) or terminate the study. |
| 2 | No SUSAR(s) 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 or SAEs 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/investigator and the SME will review the data and decide on whether it is appropriate to recommence IMP dosing (approval of a substantial amendment from the Competent Authorities is required) or terminate the study. |
| 3 | Unexpected virus-related SAE(s) or unexpected virus-related AE(s) of clinical concern have been reported following viral challenge. | If such a status occurs at any point during the study, then the PI/investigator and the SME will review the data and decide based on expectedness* of the viral event.<br>If the event is unexpected, further administration of the virus will not take place. The PI/investigator 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. |

* Expectedness will be assessed by referring to the challenge virus dossier.

A final follow-up visit will be performed on Day 28 (±3 days). Follow-up of any event should continue until resolution (return to normal or baseline values), stabilisation, it is judged by the PI/investigator to be no longer clinically significant, the participant is lost to follow-up (as defined in Section 7.3, Lost to Follow-up), or an alternative explanation has been provided (see Section 10.3.6.8., Follow-up)

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

- An unacceptable number of severe or life-threatening exacerbations of AEs take place (as determined by the PI/investigator).
- Any clinically significant life-threatening AEs, considered related to the study intervention as determined by the PI/investigator, occur.

## 7.6. Features

This study is designed to be able to utilise features to enhance study safety, efficiency, and efficacy. These design elements are predefined in their scope and limit, as detailed in Table 7-2.

The implementation of study-specific features will be documented in a non-substantial amendment. Generic features may be implemented at any time at the discretion of the PI/investigator.

**Table 7-2: Features**

| Design Category | Feature | Limit |
|---|---|---|
| **Generic** | | |
| **Cohort(s)** | 1. Participants who have been withdrawn (for any reason) may be replaced (sponsor and/or PI/investigator discretion).<br>2. Participants who are replacing a withdrawn participant may be randomised for inclusion, and dosed/challenged:<br>a. In an ongoing cohort<br>b. In a new cohort<br>c. Separately.<br>3. Any study cohort may run at the same time<br>4. The number of participants enrolled in each cohort may be reduced or increased (sponsor and/or PI/investigator discretion) to best meet the study objectives. | 1. The stopping rules of the study must be always adhered to, and replacement participants may not be enrolled to replace participants who have been withdrawn from the trial due to the meeting of stopping rules.<br>2. The total number of study participants will not exceed 100 evaluable participants.<br>3. Replacement participants will be given replacement randomisation numbers (see Section 7.4, Participant Replacement Strategy).<br>4. All protocol-defined rules and safety criteria must be met before any participant commences the study. |
| **Sample/Specimen** | 1. The PI/investigator may perform additional safety assessments, at any time, if they believe them to be clinically required.<br>2. Where clinically required (sponsor and/or PI/investigator discretion), participants may be referred for consultation(s) and/or investigation(s) under the care of a specialist physician. | 1. The maximum blood volume will not be exceeded.<br>2. Any required additional safety assessments, or specialist referrals, will be conducted on a case-by-case basis. As such the maximum number needed cannot be prospectively defined. |
| **Duration of Inpatient Stay** | 1. A participant's inpatient stay may be prolonged if discharge criteria of minimal infectiousness is not met (sponsor and/or PI/investigator discretion). | 1. Must meet the terms and criteria as detailed in the participant information sheet.<br>2. Participants must always be able to leave the study site unhindered if they wish to do so.<br>3. The additional stay is triggered based on the minimal infectiousness discharge criteria not being met (as detailed in this protocol), and the participant's suitability for residential stay will be assessed on a case-by-case basis. As such, a maximum length of stay cannot be prospectively defined. |

# 8. Study Assessments and Procedures

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

[redacted]

## 8.1. Demographics and Baseline Characteristics

### 8.1.1. Demographics

Demographic data will be recorded at the screening visit.

### 8.1.2. Height, Body Weight, and Body Mass Index

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

Body mass index will be calculated as: $BMI\ (kg/m^2) = \frac{\text{Body weight (kg)}}{\text{Height (m)}^2}$

### 8.1.3. Medical and Medication History

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

### 8.1.4. Challenge Agent 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 agent. This antibody titre cut-off for serosuitability will be described in the applicable hVIVO policy.

Serum levels of pre-existing influenza-specific antibodies will be determined using haemagglutination inhibition (HAI) influenza. Participants with results of HAI of 10 or less are eligible.

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

[redacted]

## 8.2. Respiratory Samples

The following exploratory nasal sampling procedures will be performed during the study and are detailed in the sections below:

- Nasosorption (nasal wick).
- Nasopharyngeal swab.

Where any nasal sampling time points occur together, the order of sampling will typically be (1) nasosorption followed by (2) nasopharyngeal swab, with appropriate time between sampling.

### 8.2.1. Nasosorption

A nasosorption (Class 1 Device) procedure will be used to collect samples of epithelial lining fluid for:

- Inflammatory markers (e.g., cytokines/chemokines).
- Other protein biomarkers, e.g., antibodies.
- Exploratory purposes (see Section 8.3.4, Exploratory Assessments).

Remaining epithelial lining fluid may be stored and used for exploratory purposes.

### 8.2.2. Nasopharyngeal Swab

Nasopharyngeal swabs will be performed to collect samples of nasal material for:

- Respiratory pathogen screen.
- Viral discharge test.
- Virology, i.e., viral shedding/load assessments (see Section 8.3.1, Viral Shedding/Load assessment).

Remaining material from the nasopharyngeal swabs may be stored and used for exploratory purposes.

#### 8.2.2.1. Respiratory Pathogen Screen

On entry to quarantine, a nasopharyngeal swab will be collected and tested to detect the presence of a set of respiratory pathogens that could potentially contraindicate a person's participation in the study. The methodology to be used to conduct the respiratory pathogen screen will be documented in the AP. [redacted]

[redacted]

#### 8.2.2.2. Influenza Discharge Test/Rapid Viral Antigen Test

Where required, a rapid viral antigen test (RVAT) will be used to determine the presence of influenza in a nasopharyngeal swab sample taken prior to discharge from the quarantine unit. A polymerase chain reaction (PCR) test may be used as an alternative test for this purpose, details of which will be documented in the AP. An RVAT/PCR test will be performed at the discretion of the PI/investigator and only if indicated for a clinical or other reason.

### 8.2.3. Viral Sequencing

[redacted]

## 8.3. Efficacy Assessments

### 8.3.1. Viral Shedding/Load Assessment

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

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

### 8.3.2. Participant Diary Cards

**Solicited IMP Self-assessment Diary Card**

On Days -3, -2, and -1, the solicited IMP self-assessment diary card will be completed twice daily, at 1 hour (±15 mins) and 12 hours (±30 minutes) postdose, to report the participant's experience following intranasal administration of IMP (Neumifil/placebo).

**Symptom Diary Card (Categorical)**

Participants will report and assess the severity of any challenge agent-related signs and symptoms 3 times per day starting from Day -1 (am) up to planned discharge from quarantine (Day 8, am), at the same time each day (±1 hour), using the hVIVO symptom diary card. This information will be collected using a paper form.

The following symptoms in the 11-item symptom questionnaire will be graded on a scale of 0-3 (grade 0: no symptoms; grade 1: just noticeable; grade 2: clearly bothersome from time to time but does not interfere with me doing my normal daily activities; grade 3: quite bothersome most or all of the time, and it stops me participating in activities); shortness of breath has an additional grade, i.e., grade 4: symptoms at rest.

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

**Participant Common Cold Perception Questions**

Two additional common cold-related questions will be answered by the participant each morning. The first question asks 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

### 8.3.3. 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 collection bag (for that participant only).

A daily 24-hour paper tissue collection will take place throughout the quarantine period. Distribution of paper tissues and collection bags will start in the morning on Day -1, with the first collection on Day 0. Thereafter, distribution and collection of tissues will occur daily, at the same time point (±1 hour) in the morning ,with tissues distributed 24 hours ahead, until discharge from quarantine.

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 tissues used for nose blowing or sneezing over each 24-hour period.

### 8.3.4. Exploratory Assessments

Cytokine and chemokine proteomic profile and/or messenger RNA profile will be assessed for associations with Neumifil response, and other endpoints.

## 8.4. Safety Assessments

### 8.4.1. Complete Physical Examination

A complete physical examination to include a full systemic assessment.

### 8.4.2. Symptom-directed Physical Examination

Symptom-directed physical examinations will be conducted as deemed appropriate by the PI/investigator and may include (as applicable) examination of the eyes, ears, nose, throat, and respiratory system/chest. Based upon the presence or absence of clinical signs and symptoms, PI/investigator discretion will be used to determine the requirement to perform certain ongoing assessments.

[redacted]

### 8.4.3. Vital Signs and Tympanic Temperature

Vital signs assessments will be recorded [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Study-specific normal ranges for vital signs and tympanic temperature are provided in Appendix 4, Normal Ranges.

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 sponsor requirements using the Food and Drug Administration (FDA) toxicity grading scale (FDA Guidance document for Industry, 2007).

[redacted]

[redacted]

[redacted]

[redacted]

### 8.4.4. Electrocardiogram

Study-specific normal ranges are provided in Appendix 4, Normal Ranges.

[redacted]

[redacted]

### 8.4.5. Clinical Safety Laboratory Assessments

#### 8.4.5.1. Urinalysis

Clinical urine safety analysis will be undertaken using commercially available urine test strips (i.e., dipsticks) that provide an instant result, which will be documented in the source data.

Urinalysis will be performed to evaluate the parameters described in Appendix 2, Clinical Laboratory Tests.

[redacted]

#### 8.4.5.2. Drugs of Misuse and Cotinine

[redacted]

#### 8.4.5.3. Alcohol Breath Testing

[redacted]

#### 8.4.5.4. Safety Blood Analysis and Assessments

[redacted]

### 8.4.6. Pregnancy Tests and Follicle-stimulating Hormone

[redacted]

### 8.4.7. Lung Function

**Spirometry**

[redacted]

## 8.5. Recording of Adverse Events/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, hVIVO SOPs, and the study-specific protocol. The PI/investigator is also responsible 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/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, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

### 8.5.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs/SAEs will be collected from signing of the study-specific ICF until the last scheduled follow-up visit.

Investigators are not obligated to actively seek AEs/SAEs after conclusion of study participation. However, if the PI/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 PI/investigator must promptly notify the sponsor.

### 8.5.2. Method of Detecting Adverse Events/Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs/SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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

### 8.5.3. Follow-up of Adverse Events/Serious Adverse Events

[redacted]

### 8.5.4. Regulatory Reporting Requirements for Serious Adverse Events

Any SAE will be reported immediately by the PI/investigator to the sponsor and the SME or sponsor's pharmacovigilance vendor (in practice reporting within 24 hours of the PI/investigator's knowledge of the event). [redacted]

### 8.5.5. Pregnancy

[redacted]

[redacted]

## 8.6. Bioanalysis/Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of Neumifil as specified in the SoE.

A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the PI/investigator and the sponsor. The timing of sampling may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the plasma concentrations of Neumifil. Samples collected for analyses of Neumifil plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

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

### 8.6.1. Pharmacokinetic Blood Samples

Neumifil plasma concentrations will be measured and may be used to assist in evaluating the efficacy of Neumifil. A full PK investigation is not planned for this study. Blood samples for measurement of plasma concentrations of Neumifil will be collected in accordance to the SoE and plasma will be sent to sponsor's PK vendor according to the AP.

Blood samples for measurement of plasma concentrations of Neumifil will be collected on Days -3, -2, and -1 at the following time points: predose (within 2 hours before IMP administration) and 1, 2, and 3 hours (±15 mins) postdose.

### 8.6.2. Pharmacokinetic Parameters

Pharmacokinetic parameters of interest may include:

$AUC_{0-t}$, $AUC_{0-\infty}$, $C_{max}$, $t_{max}$, $t_{1/2}$

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

A full PK investigation is not planned for this study. Neumifil plasma concentrations will be measured and may be used to assist in evaluating the efficacy of Neumifil.

### 8.6.3. Anti-drug Antibodies

Serum samples will be collected to measure the incidence of anti-drug antibodies (ADAs) to Neumifil during the study.

## 8.7. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

## 8.8. Immunogenicity Assessments

Blood will be collected for immunological analysis.

Humoral immune responses, e.g., haemagglutination inhibition (HAI) will be evaluated in serum samples collected from all participants according to the SoE.

[redacted]

## 8.9. Genetics

[redacted]

## 8.10. Biomarkers

Collection of samples for biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoE:

- Nasosorption
- Serum

[redacted]

### 8.10.1. Immunology Biomarker Evaluations

Blood will be taken for exploratory immunology and genomic analysis related to viral infection/study intervention(s), including but not limited to:

- Influenza antibodies

- Immunoglobulin [Ig] A [IgA] and G [IgG] antibodies
- PAXgene RNA

Sample processing, storage, and assessments will be detailed in the AP.

# 9. Statistical Considerations

## 9.1. Statistical Hypothesis

The primary statistical hypothesis is that prophylactic treatment with Neumifil will significantly reduce the incidence and/or the severity of symptomatic influenza infection after influenza viral challenge when compared to placebo. Individual comparisons of each Neumifil dose arm to the placebo arm will be performed with an exploratory purpose. No adjustment for multiple comparisons will be performed.

## 9.2. Sample Size Determination

The sample size is based on the primary comparison of the 2 active treatment arms pooled to the placebo arm. The study has not been powered for the comparisons between each active treatment arm to the placebo arm and these comparisons will be presented for exploratory purposes. Nevertheless, for some of the endpoints, a power above 80% is achieved for these comparisons.

The number of 40 participants in the placebo arm and 60 (30 in each dose arm) in the pooled Neumifil group selected for this study will provide a power of at least 80% to detect a significant reduction in the primary endpoints:

- of 70% compared to the placebo arm in symptomatic influenza infection rate, assuming a symptomatic infection rate of 27.8% in the placebo arm,
- of 65% compared to the placebo arm in peak TSS, assuming a coefficient of variation (CV) of 125%,

using a 1-sided 0.05 type-one error rate for each of the 2 comparisons, without adjustment for multiple testing.

The table below summarises the power achieved with 40 versus 60 participants (for the placebo and pooled active treatment arms, respectively) for the 2 primary endpoints and some secondary endpoints.

| Endpoint | Assumption (placebo arm) | Relative reduction | Power (*) |
|---|---|---|---|
| **Symptomatic infection rate** | **rate=27.8%** | **70%** | **81.5%** |
| **Peak TSS** | **CV=125%** | **65%** | **81.2%** |
| VL-AUC | CV=91% | 50% | 84.8% |
| VLPEAK | CV=63.5% | 40% | 92.2% |
| TSS-AUC | CV=155% | 80% | 80.7% |

(*) Power achieved with placebo and 60 Neumifil participants (alpha 0.05 1-sided).
CV = coefficient of variation.

Corresponding power calculations for the comparison of the placebo arm (40 participants) to one of the 2 Neumifil dose arms (30 participants) are provided below:

| Endpoint | Assumption (placebo arm) | Relative reduction | Power (*) |
|---|---|---|---|
| **Symptomatic infection rate** | **rate=27.8%** | **70%** | **66.6%** |
| **Peak TSS** | **CV=125%** | **65%** | **68.7%** |
| VL-AUC | CV=91% | 50% | 72.8% |
| VLPEAK | CV=63.5% | 40% | 82.6% |
| TSS-AUC | CV=155% | 80% | 68.1% |

(*) Power achieved with placebo and 30 Neumifil participants (alpha 0.05 1-sided).
CV = coefficient of variation.

## 9.3. Populations for Analyses

The study populations are defined in Table 9-1.

**Table 9-1: Study Populations**

| Population | Description |
|---|---|
| Enrolled | All participants who have been randomised.<br>Potential participants who are screened for the purpose of determining suitability for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. |
| Intent-to-treat (ITT) analysis set | All participants randomised, having received at least 1 dose of IMP, and challenged with the study virus. |
| Intent-to-treat infected (ITT-I) analysis set | All participants randomised, having received at least 1 dose of IMP, and challenged with the challenge virus, and who were infected with challenge virus as per the definition of laboratory-confirmed infection. |
| Per protocol (PP) analysis set | All participants randomised, having received the planned dose of IMP (Neumifil 3 doses on Days -3 to -1, 1 single dose of Neumifil on Day -3 followed by 2 doses of placebo on Days -2 and -1; or placebo 3 doses on Days -3 to -1, according to randomisation) and challenged with the study virus, who complete the quarantine period up to its planned final day (Day 8) and present no major deviation likely to impact the evaluation of the primary efficacy endpoint. |
| Safety analysis set | All participants randomised having received at least 1 dose of IMP. Participants will be analysed according to the intervention (multiple dose Neumifil, single dose Neumifil, placebo) they received. |
| PK analysis set | All participants randomised having received at least 1 dose of IMP, with at least 1 postdose PK result. |

Membership of participants in each analysis set will be determined at a planned data review meeting, prior to any analysis and database lock.

The primary efficacy analysis will be on the PP analysis set. The ITT analysis set 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.

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

### 9.4.1. Statistical Analysis Plan

The SAP will be developed and finalised prior to database lock for the study. The finalised SAP will be signed prior to unblinding the study 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 analysis.

Any deviation(s) from the original statistical plan outlined in the protocol will be described and justified in an amendment to the protocol and/or SAP, as appropriate, and referenced in the final clinical study 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 number of available data, number of missing data, mean (and/or geometric mean, where applicable), standard deviation, median, lower quartile, upper quartile, minimum, and maximum values. When relevant, confidence intervals (CIs) will be computed for the mean and/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-arm comparisons will be performed using appropriate hypothesis tests at the 5% 1-sided significance level, except if otherwise specified. No adjustment for multiple testing will be performed (see Section 9.1, Statistical Hypothesis).

The main analyses will be the ones comparing the 2 active treatment arms pooled to the placebo arm. These analyses will be repeated with an exploratory purpose to the comparison of each Neumifil arm to the placebo.

For continuous variables (either raw data or log-transformed data) the difference in means, the standard error and the 90% and 95% 2-sided CIs 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 90% and 95% 2-sided CIs for the original variable will be presented. The Wilcoxon rank sum test, 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 90% and 95% 2-sided CIs. Except otherwise specified in the SAP, the Chi-square test (or Fisher exact test) will be used to compare frequencies between study intervention arms.

### 9.4.3. Planned Analysis

#### 9.4.3.1. Participant Accountability

The number of participants receiving challenge agent, receiving IMP (Neumifil/placebo), withdrawing from (also split by reason for withdrawal), and completing the study, and the numbers in each analysis set, will be summarised.

#### 9.4.3.2. Protocol Deviations

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

#### 9.4.3.3. Demographic and Baseline Characteristics

Descriptive statistics of demographics (age, sex, height, body weight, BMI, and ethnicity) will be presented by study intervention arm (each individual dose arm, the pooled Neumifil arms, and the placebo arm) 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

For each participant, the proportion of the planned dose actually received will be computed.

Compliance with IMP (Neumifil/placebo) will be computed for each study intervention arm as the proportion of participants actually receiving IMP as prescribed (i.e., 100% of the planned dose has been received).

### 9.4.4. Primary Efficacy Analysis

The primary efficacy analysis will be conducted on the per protocol (PP) analysis set (Section 9.3, Populations for Analyses).

For the symptomatic infection rate, the estimator with its 2-sided 90% and 95% CIs will be presented by treatment arm. The differences between the pooled active treatment arms and the placebo arm, and between each active treatment dose arm and the placebo arm, will be computed with their 2-sided 90% and 95% CIs. The 3 pairwise comparisons will use the Pearson Chi-square test, or the Fisher exact test if the assumptions for the Chi-square test are not met. Each test will use a nominal 1-sided type-one error of

0.05 without adjustment for multiplicity. In addition, the difference between the 2 Neumifil dose arms will be computed with its 90% and 95% CIs but no formal statistical test will be computed.

For the peak TSS, the mean and median and the 2-sided 90% and 95% CIs for the mean will be presented by treatment arm. The differences between the pooled active treatment arms and the placebo arm, and between each active treatment dose arm and the placebo arm, will be computed with their 2-sided 90% and 95% CIs. The 3 pairwise comparisons will use the Wilcoxon rank-sum test. Each test will use a nominal 1-sided type-one error of 0.05 without adjustment for multiplicity. In addition, the difference between the 2 Neumifil dose arms will be computed with its 90% and 95% CIs but no formal statistical test will be computed.

Further details on the primary efficacy analysis will be provided in the SAP.

### 9.4.5. Secondary Efficacy Analysis

Secondary endpoints as outlined in Section 3, Objectives and Endpoints, will be summarised by study intervention arm as described in Table 9-2. Further details on the secondary efficacy analysis will be provided in the SAP.

**Table 9-2: Methods for Analysis of Secondary Efficacy Endpoints**

| Endpoint | Analysis |
|---|---|
| TSS-AUC | Descriptive statistics for continuous variables by treatment arm (Section 9.4.2, General Considerations).<br>Inferential analysis: pairwise t-tests or Wilcoxon rank sum tests. |
| Peak viral load by qRT-PCR | Descriptive statistics for continuous variables (Section 9.4.2, General Considerations).Inferential analysis: Wilcoxon rank sum test. |
| Peak daily symptom score | Descriptive statistics for continuous variables (Section 9.4.2, General Considerations).<br>No inferential analysis. |
| Number (%) of participants with grade 2 or higher symptoms, starting from Day 1 (am) up to planned discharge from quarantine (Day 8, am) | Descriptive statistics for categorical variable variables (Section 9.4.2, General Considerations).<br>Inferential analysis: pairwise Chi-square tests (or Fisher exact tests). |
| Duration of clinical symptoms: 1) any symptoms. | Descriptive statistics for continuous variables (Section 9.4.2, General Considerations).<br>No inferential analysis. |
| Duration of clinical symptoms: 2) TSS of 2 or more (with at least 2 systems) | |

| | |
|---|---|
| Duration of clinical symptoms: 3) grade 2 or higher symptoms | |
| Time to resolution from peak clinical symptoms | Descriptive statistics for continuous variables (Section 9.4.2, General Considerations).<br>Kaplan Meier curves will be prepared.<br>No inferential analysis. |
| Area under the qRT-PCR viral load-time curve (VL-AUC) | Descriptive statistics for continuous variables by treatment arm (Section 9.4.2, General Considerations).Inferential analysis: pairwise t-tests or Wilcoxon rank sum tests. |
| Area under the tissue culture viral load-time curve (VL-AUC) | |
| VLPEAK (qRT-PCR) | |
| VLPEAK (tissue culture) | |
| Duration of quantifiable influenza (qRT-PCR) | Descriptive statistics for continuous variables (Section 9.4.2, General Considerations).<br>No inferential analysis. |
| Duration of quantifiable influenza (tissue culture) | |
| Duration of detectable influenza (tissue culture) | |
| Time to resolution from VLPEAK by qRT-PCR | Descriptive statistics for continuous variables (Section 9.4.2, General Considerations).<br>Kaplan Meier curves will be prepared.<br>No inferential analysis. |
| Time to resolution from VLPEAK by quantitative viral culture | |
| Total weight of mucus produced | Descriptive statistics for continuous variables (Section 9.4.2, General Considerations).<br>No inferential analysis. |
| Total number of tissues used | |
| Incidence of RT-PCR-confirmed influenza infection, defined as 2 quantifiable (≥ LLOQ) qRT-PCR measurements (reported on 2 or more independent nasal samples over 2 days)* | Descriptive statistics for categorical variable variables (Section 9.4.2, General Considerations).<br>Inferential analysis: pairwise Chi-square tests (or Fisher exact tests). |
| Occurrence of at least 1 positive quantitative (≥ LLOQ) cell culture measurement in nasal sample | |

| | |
|---|---|
| Incidence of cell culture-confirmed symptomatic influenza infection | |
| Number (%) of participants with lab-confirmed infection and fever (≥37.9°C) | |

LLOQ = lower limit of quantification; (q)RT-PCR = (quantitative) reverse transcriptase polymerase chain reaction; TSS = total symptoms score; TSS-AUC = area under the curve over time of total symptoms score; VL-AUC = area under the viral load-time curve; VLPEAK = peak viral load.
* Additional sensitivity analyses using alternative definitions for symptomatic infections may be added in the Statistical Analysis Plan (SAP).

### 9.4.6. Tertiary/Exploratory Analysis

Tertiary/exploratory endpoints as outlined in Section 3, Objectives and Endpoints, will be summarised by study intervention arm. Further details are described in the SAP.

### 9.4.7. Safety Analyses

All safety analyses will be computed on the safety analysis set.

Unless otherwise stated, safety endpoints will be presented in terms of descriptive statistics only.

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

[redacted]

Further details on the safety analyses will be provided in the SAP.

### 9.4.8. Bioanalysis/Plasma Concentrations

Descriptive statistics will be calculated for the plasma concentrations of Neumifil at each applicable time point and for the derived plasma PK parameters. Statistics include sample size (n), mean, standard deviation, coefficient of variation (CV), geometric mean, median, minimum, and maximum.

For each participant, plasma concentration-time data of Neumifil will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced.

Additional PK analyses may be performed as deemed necessary.

The details of the PK analyses will be provided in a separate PK analysis plan.

## 9.5. Interim Analysis

No interim analyses are planned for this study.

## 9.6. Data Monitoring Committee

Not applicable.

# 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 Organisations of Medical Sciences International Ethical Guidelines.
- Applicable ICH Good Clinical Practice (GCP) guidelines.
- Applicable laws and regulations.

[redacted]

[redacted]

The PI/investigator will be responsible for the following:

- Providing written summaries of the status of the study to the REC annually, or more frequently, in accordance with the requirements, policies, and procedures established by the REC.
- Notifying the REC of SAEs or other significant safety findings as required by REC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the REC, the REC, UK SI 2004/1031 The Medicines for Human Use (Clinical Trials) Regulations, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

### 10.1.2. Financial Disclosure

[redacted]

### 10.1.3. Confidentiality

The PI/investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

### 10.1.4. Informed Consent Process

The trained and delegated study staff competent to perform the informed consent procedure will obtain a signed study-specific ICF from each participant before any study-specific procedures are performed.

Historical screening data may be collected through the hVIVO generic screening process, which is a comprehensive assessment of health status including previous medical history. For assessments taken under the hVIVO generic screening, a separate informed consent is obtained.

When historical screening data collected through the hVIVO generic screening process is used for screening, the study-specific ICF will be obtained at the first study-specific visit from each participant before any study-specific procedures are performed.

Potential participants will typically be sent a copy of the REC approved study-specific ICF at the time of invite to the first study-specific visit 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 study-specific ICF is discussed by the trained and delegated study staff competent to perform the informed consent procedure, and the participants 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 PI/investigator will be responsible for ensuring that the participant understands the information contained in the ICF. Once the PI/investigator has confirmed that the participant has capacity and has understood the study, including the benefits and risks of participation, the participant and the PI/investigator can sign and date the study-specific ICF.

The study-specific ICF must be signed and dated by the participant and countersigned by the trained and delegated study staff competent to perform the informed consent procedure (whoever conducted the consent discussion). A copy of the study-specific 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 study-specific ICF.

The study-specific ICF will contain a separate section that addresses the use of samples for future research. The PI/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 (with no requirements to disclose the reason for withdrawal) and may withdraw their consent at any time and for any reason.

### 10.1.5. Data Protection

Participants will be assigned a unique identifier by hVIVO. Any participant records or datasets that are transferred to the sponsor 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 the ICF.

The participant must be informed that his/her medical records may be examined by clinical quality assurance auditors or other authorised study staff appointed by the sponsor, by appropriate REC members, and by inspectors from regulatory authorities.

### 10.1.6. Committee(s) Structure

This study will not include an early safety data review.

### 10.1.7. Dissemination of Clinical Study Data

The key design elements of this protocol will be posted on publicly accessible registry. [redacted]

### 10.1.8. Data Quality Assurance

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

The PI/investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. This can be paper source and/or eSource.

The PI/investigator must permit study-related monitoring, audits, REC review, and regulatory agency inspections and provide direct access to source data documents. [redacted]

### 10.1.9. 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.

[redacted]

### 10.1.10. Study Discontinuation

The sponsor reserves the right to temporarily suspend or terminate the study for any reason at any time. In addition, the study may be temporarily put on hold or terminated at any time if, in the opinion of the PI/investigator, the safety data suggest that the medical safety of participants is being compromised.

[redacted]

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

### 10.1.11. Publication Policy

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

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

If the study is to be published, the sponsor and hVIVO may jointly prepare and co-author manuscript(s) that could result from the clinical study. In the case the sponsor acts as fully responsible for the publication, the sponsor agrees to allow the PI/investigator 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.

## 10.2. Appendix 2: Clinical Laboratory Tests

[redacted]

[redacted]

[redacted]

[redacted]

| [redacted] | [redacted] |
|---|---|
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| [redacted] | [redacted] |
| [redacted] | [redacted] |

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| [redacted] | [redacted] |
| [redacted] | [redacted] |

[redacted]

[redacted].

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

## 10.3.1. Adverse Event

**Adverse Event Definition**

[redacted]

**Solicited Adverse Events**

[redacted]

- [redacted]
- [redacted]

**Unsolicited Adverse Events**

[redacted]

**Events Meeting the Adverse Event Definition**

- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]

**Events NOT Meeting the Adverse Event Definition**

- [redacted]

### 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 PI/investigator or the sponsor as having a reasonable causal relationship to an IMP 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 adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:

a) In the case of a product with a marketing authorisation, in the Summary of Product Characteristics for that product,
b) In the case of any other IMP, in the Investigator's Brochure relating to the study in question.

### 10.3.4. Serious Adverse Event

| **Serious Adverse Event Definition** |
|---|
| **A Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:** |
| **a. Results in death** |
| **b. Is life-threatening** [redacted] |
| **c. Requires inpatient hospitalisation or prolongation of existing hospitalisation** • [redacted] |
| **d. Results in persistent disability/incapacity** • [redacted] |
| **e. Is a congenital anomaly/birth defect** |

**f. Is an important medical event**

- [redacted]

[redacted]

### 10.3.5. Suspected Unexpected Serious Adverse Reaction

A SUSAR is a serious adverse reaction, the nature and severity* of which is not consistent with the information about the medicinal product in question, as defined in the Investigator's Brochure relating to the study in question.

[redacted]

### 10.3.6. Recording, Assessment, and Follow-up of Adverse Events/Serious Adverse Events

#### 10.3.6.1. Adverse Event/Serious Adverse Event Recording

All AEs/SAEs will be collected from the time of written study-specific informed consent until study completion/final study contact or until the resolution of the AE. [redacted]

[redacted]

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

- [redacted]

[redacted]

### 10.3.6.2. Assessment

Description

[redacted]

Onset and end

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

| Assessment |
| --- |
| **Challenge Agent-related Symptoms**<br>[redacted] |
| **Physical Examination**<br>[redacted] |
| **Symptom-directed Physical Examination**<br>[redacted] |
| **Vital Signs**<br>[redacted] |
| **Temperature**<br>[redacted] |
| **Spirometry**<br>[redacted] |

[redacted].

**Laboratory Values**

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

### 10.3.6.3. Assessment of Intensity

[redacted]

[redacted]

[redacted]

**Table 10-2: 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 one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

### 10.3.6.4. Frequency

[redacted]

### 10.3.6.5. Assessment of Causality

[redacted]

- The PI/investigator may change his/her opinion of causality considering follow-up information and send an 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 10-3.

**Table 10-3: Classification of Adverse Events Relationship**

| Classification | Definition |
|---|---|
| Not related | [redacted] |
| Unlikely to be related | [redacted] |
| Definitely related | [redacted] |
| Possibly related | [redacted] |
| Probably related | [redacted] |

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

### 10.3.6.6. Action Taken

[redacted]

- [redacted]

- [redacted]

### 10.3.6.7. Outcome

[redacted]

**Table 10-4: Classification of Adverse Events Outcome**

| Classification | Definition |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

### 10.3.6.8. Follow-up

[redacted]

[redacted]

[redacted]

### 10.3.7. Reporting of Serious Adverse Events

Serious AEs must be documented and reported as per hVIVO SOPs.

[redacted]

**Table 10-5: Contact Details for Reporting All Serious Adverse Events**

| Contact | Details |
|---|---|
| Name of sponsor's medical expert (SME): | [redacted] |
| SME SAE telephone number: | [redacted] |
| Pharmacovigilance reporting email: | [redacted] |
| Pharmacovigilance telephone reporting: | [redacted] |
| SAE email address: | pvservices@propharmagroup.com<br>(cc to [redacted]) |

[redacted]

[redacted]

### 10.3.11. Pregnancy

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

## 10.4. Appendix 4: Normal Ranges

[redacted]

| [redacted] | | | |
|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] |
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[redacted]

## 10.5. Appendix 5: Genetics

[redacted]

## 10.6. Appendix 6: Abbreviations

| Abbreviation | Term |
|---|---|
| ADA | Anti-drug antibody |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| AP | Analytical plan |
| $AUC_{0-\infty}$ | Area under the concentration-time curve from time zero to infinity |
| $AUC_{0-t}$ | Area under the concentration-time curve from time zero to time t |
| BD | Twice daily |
| β-hCG | β-human chorionic gonadotrophin |
| BMI | Body mass index |
| CBM | Carbohydrate binding module |
| (c)GMP | (current) Good Manufacturing Practice |
| CI | Confidence interval |
| $C_{max}$ | Maximum observed concentration |
| COVID19 | Coronavirus Disease 2019 |
| CRF | Case report form |
| CV | Coefficient of variation |
| CYP | Cytochrome P450 |
| DBP | Diastolic blood pressure |
| DNA | Deoxyribonucleic acid |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| FDA | Food and Drug Administration |
| $FEV_{(1)}$ | Forced expiratory volume (in 1 second) |
| FSH | Follicle-stimulating hormone |
| FVC | Forced vital capacity |
| GAD | Generalised Anxiety Disorder |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GP | General practitioner |
| HAI | Haemagglutination inhibition |
| HIV | Human immunodeficiency virus |
| ICF | Inform consent form |
| ICH | International Council for Harmonisation |
| Ig | Immunoglobulin |
| IgA | Immunoglobulin A |
| IgG | Immunoglobulin G |
| IMP | Investigational medicinal product |
| ITT | Intent-to-treat |
| ITT-I | Intent-to-treat infected |
| IWRS | Interactive Web Response System |
| LLOD | Lower limit of detection |
| LLOQ | Lower limit of quantification |
| LRT | Lower respiratory tract |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NOAEL | No observed adverse effect level |
| PCR | Polymerase chain reaction |
| PHQ | Patient Health Questionnaire |
| PI | Principal investigator |

| | |
|---|---|
| PK | Pharmacokinetic |
| PP | Per protocol |
| (q)RT-PCR | (Quantitative) reverse transcriptase polymerase chain reaction |
| REC | Research Ethics Committee |
| RNA | Ribonucleic acid |
| RSV | Respiratory syncytial virus |
| RVAT | Rapid viral antigen test |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SBP | Systolic blood pressure |
| SME | Sponsor's medical expert |
| SoE | Schedule of events |
| SOP | Standard operating procedure |
| $SpO_2$ | Peripheral arterial oxygen saturation |
| SUSAR | Suspected unexpected adverse reaction |
| $T_{1/2}$ | Terminal half-life |
| $TCID_{50}$ | Tissue culture infective dose (50%) |
| TD | Trimerisation domain |
| $T_{max}$ | Time to maximum concentration |
| TMF | Trial master file |
| TSS | Total symptoms score |
| TSS-AUC | Area under the curve over time of total symptoms score |
| UK | United Kingdom |
| URT | Upper respiratory tract |
| VL-AUC | Area under the viral load-time curve |
| VLPEAK | Peak viral load |
| WHO | World Health Organisation |

## 10.7. [redacted]

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## 10.8. Appendix 8: Protocol Amendment History

| Protocol History | | | |
|---|---|---|---|
| **Version** | **Date** | **Amendment Type and Number** | **Description of Change** |
| 2.0 | 20Jul2022 | N/A | Initial Clinical Trial Protocol |
| 3.0 | 12Feb2023 | Non-Substantial Amendment 02 | Update made to Section 1, Protocol Synopsis, Section 4.1, Overall Design and Section 7.6, Features, Table 7-2 for clarification that the total number of participants enrolled into the study will be up to 100 evaluable volunteers.<br><br>[redacted] |

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