# Pneumagen Ltd

# Trial Protocol

**Confidential**

| | |
|---|---|
| **Trial title** | A two-part, randomised, double-blind, placebo-controlled, ascending dose study to assess the safety and tolerability of single and multiple doses of Neumifil (a novel drug candidate with potential for treatment of COVID-19). |
| **Short title** | Safety and tolerability of single and repeated doses of Neumifil |
| **Version and date of protocol** | Version 3, dated 15 December 2021 |
| **HMR code** | 20-021 |
| **Sponsor code** | PNG-NMF-101 |
| **EudraCT no** | 2021-001946-36 |
| **Trial medication** | Neumifil |
| **Phase of trial** | Phase 1 |
| **Place of trial** | HMR<br>Cumberland Avenue<br>London NW10 7EW<br>Tel: 020 8961 4130<br>Fax: 020 8961 8665 |
| **Principal investigator** | [redacted]<br>HMR |
| **Sponsor** | Pneumagen Ltd<br>Kinburn Castle, Doubledykes Road<br>St. Andrews, Fife<br>Scotland KY16 9DR<br>Tel: [redacted]<br>Email: [redacted] |
| **Planned dates of trial** | October 2021 to February 2022 |

# 1 Signatures

The investigator and the sponsor have discussed this protocol. The investigator agrees to perform the investigation and to abide by this protocol and any future agreed amendments, except in case of medical emergency.

**Principal investigator**

[redacted]
HMR

**Statistician**

[redacted]
HMR

**Sponsor**

[redacted]
Pneumagen CMO (consultant)

[redacted]

# 2 Summary

## 2.1 Trial medication

Neumifil is a first-in-class, multivalent, glycan-targeting carbohydrate binding module (CBM). It is being developed as a nasal formulation to treat viral respiratory tract infections (RTIs), including those caused by SARS-CoV-2.

## 2.2 Objectives

### *2.2.1 Primary objectives*

*Part A*

- To assess the safety and tolerability of single-ascending intranasal doses of Neumifil in healthy subjects.

*Part B*

- To assess the safety and tolerability of multiple-ascending intranasal doses of Neumifil in healthy subjects.

### *2.2.2 Exploratory objective*

- To determine the number of subjects contracting SARS-CoV-2 during the 7 days after receiving their (last) dose.
- To assess the formation of Neumifil anti-drug antibodies (ADAs) after multiple-ascending intranasal doses in healthy subjects (Part B only).
- To assess plasma concentration of single- or multiple-ascending intranasal doses of Neumifil in healthy subjects to determine if intranasal administration results in systemic exposure.
- To assess the concentrations of cytokines and chemokines in nasal secretions before dosing and after multiple intranasal doses of Neumifil (Part B only).

## 2.3 Endpoints

### *2.3.1 Primary endpoints*

*Safety and tolerability*:

Clinically significant changes in: vital signs (heart rate, blood pressure, respiratory rate, pulse oximetry, and temperature), 12-lead electrocardiogram (ECG), forced expiratory volume ($FEV_1$), forced vital capacity (FVC), physical examination, nasal examination, laboratory safety tests (haematology, biochemistry and urinalysis), tolerability questionnaire, number and severity of adverse events (AEs) and serious AEs. Safety endpoints will be assessed up to 7 days after dosing in Part A or up to 14 days after the last dose in Part B.

### *2.3.2 Exploratory endpoint*

*PD:* SARS-CoV-2 infection test, done at screening, before the first dose, on Day 8 (Part B only), and at follow-up.

*Immunogenicity:* ADAs of Neumifil, as assessed by immunoglobulin A and G (IgA and IgG) concentration, derived from blood samples taken before the first dose and at follow-up (Part B only).

*Plasma concentrations of Neumifil:* Plasma concentrations of Neumifil after single doses on Day 1 in Part A, and after dosing on Days 1 and 7 in Part B.

*Cytokine and chemokine concentrations in nasal secretions:* Presence and concentration of cytokines and chemokines, measured by multiplex assay, in nasal wick samples collected on Day –1, Day 8, and at follow up (Part B only).

## 2.4 Type of trial

This is a Phase 1, single-centre, randomised, placebo-controlled first-time-in-human (FTIH) study in healthy subjects. The study is in 2 parts and will investigate single-ascending (Part A) and multiple-ascending (Part B) doses of Neumifil, administered intranasally.

## 2.5 Trial design and methods

### *2.5.1 Part A*

Part A is a randomised, double-blind, placebo-controlled, single ascending dose study. Enrolment of up to 36 healthy subjects is planned, in up to 5 groups (Groups A1−A5). Groups A1–A3 will consist of 6 subjects each and Groups A4 and A5 will consist of 9 subjects each.

Subjects will receive a single intranasal dose of Neumifil or placebo. In Groups A1−A3, 4 subjects will receive Neumifil and 2 will receive matching placebo. In Groups A4 and A5, 6 subjects will receive Neumifil and 3 will receive matching placebo.

The planned dose levels are: 0.028 mg (Group A1), 0.085 mg (Group A2), 0.28 mg (Group A3), 0.885 mg (Group A4), and 2.8 mg (Group A5). Because Neumifil has never been given to humans before, each new ascending dose will be staggered via the use of sentinel subjects. It is intended that subsequent groups will receive higher doses. The dose will be escalated only if the safety and tolerability of the previous highest dose are acceptable, as determined by the Safety Review Group (SRG). Additional dose levels may be explored in up to 2 optional groups of 9 subjects (Groups A6 and A7).

Subjects will be screened within 35 days before their dose of trial medication. Subjects will be resident on ward from 1 day before their dose (Day –1) until about

24 h after dosing (Day 2). They will return for a follow-up visit 7–8 days after their dose (Day 8–9).

### *2.5.2 Part B*

Part B is a randomised, double-blind, placebo-controlled, multiple ascending dose study.

Enrolment of up to 24 healthy subjects is planned, in up to 3 groups (Groups B1−B3) of 8 subjects each. Subjects will receive once-daily intranasal doses of Neumifil or placebo for 7 days. In each group, 6 subjects will receive Neumifil and 2 will receive matching placebo.

Part B can start before completion of Part A. The starting dose level (dose and dose regimen) for Group B1 will be decided after review of safety and tolerability data from at least 3 dose levels in Part A and will be no higher than a dose level that has previously been shown to cause no safety concerns in Part A (see section 8.5.3). Subsequent dose levels will be determined as described for Part A. An additional dose level may be explored in 1 optional group (Group B4).

Subjects will be screened within 35 days before their dose of trial medication. Subjects will be resident on ward from 1 day before their dose (Day –1) until about 24 h after their last dose (Day 8). Subjects will attend an outpatient visit at 7−8 days after their last dose (Days 15–16). They will then return for a follow-up visit at 13−15 days after their last dose (Days 21–23).

## 2.6 Trial population

a **Total** Up to 60 healthy volunteers (up to 36 in Part A and up to 24 in Part B), excluding replacements

b **Age** 18–60 years

c **Inclusion criteria**

Normotensive male or female volunteers, deemed healthy on the basis of a clinical history, physical examination, ECG, vital signs, and laboratory tests of blood and urine; body mass index (BMI; Quetelet index) in the range 18.0–30.9 kg/m$^2$; non-smoker; $FEV_1$ and FVC ≥ 80%; agree to follow the contraception requirements of the trial (section 11); agree not to donate blood or blood products during the study and for 3 months after dosing; able to give fully informed written consent.

d **Exclusion criteria**

Positive tests for hepatitis B & C, human immunodeficiency virus (HIV); severe adverse reaction to any drug; sensitivity to trial medication; known allergy to tetracycline antibiotics; drug or alcohol abuse, or regular intake of > 14 units of alcohol weekly; evidence of smoking in the last 3 months; use of over-the-counter

medication (with the exception of paracetamol, or vitamin or nutritional supplements) during the 7 days, or prescribed medication (with the exception of hormone replacement therapy [HRT]), including oral contraceptives, during the 28 days, before the first dose of trial medication; receipt of a COVID-19 vaccine during the 7 days before the first dose of trial medication, or anticipate receiving a COVID-19 vaccine within the 7 days after a (final) dose of trial medication; participation in other clinical trials of unlicensed medicines, or loss of more than 400 mL blood, within the previous 3 months; vital signs and ECG measurements outside the acceptable range; clinically relevant abnormal findings at the screening assessment; acute or chronic illness; clinically relevant abnormal medical history (including psychiatric disease or cancer) or concurrent medical condition (including respiratory disease or illness); immune suppressed status, resulting from disease or medication; possibility that volunteer will not cooperate; females who are pregnant or lactating, or who are sexually active and not using a reliable method of contraception (section 11); objection by general practitioner (GP) to trial participation.

## 2.7 Assessments

The following assessments will be made.

### *2.7.1 Safety and tolerability*

Laboratory assessments (haematology, biochemistry and urinalysis), physical examinations, 12-lead ECGs, vital signs (heart rate, blood pressure, respiratory rate, pulse oximetry and temperature), nasal examinations, $FEV_1$ and FVC will be done before and during dosing and frequently until the subject's last visit in each study part. Subjects will complete a tolerability questionnaire after each dose of Neumifil. AEs will be recorded from screening until the subject's last visit in each study part.

### *2.7.2 Pharmacokinetics*

Blood samples for assay of Neumifil will be taken before and up to 3 h after dosing on Day 1 (Part A) and Days 1 and 7 (Part B).

### *2.7.3 Immunogenicity*

Blood samples for assay of Neumifil ADAs will be taken before dosing on Day 1, and on Day 22 (Part B only).

### *2.7.4 Pharmacodynamics*

Nasal wick samples for assay of cytokines and chemokines in nasal secretions

[redacted]

# 3 Contents

## 3.1 Table of figures



## 3.2 Table of tables

# 4 List of abbreviations

| | |
|---|---|
| ABPI | Association of the British Pharmaceutical Industry |
| ACE2 | angiotensin-converting enzyme 2 |
| ADA | anti-drug antibodies |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AP | alkaline phosphatase |
| AR | adverse reaction |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| $AUC_{inf}$ | area under the concentration–time curve extrapolated to infinite time |
| BMI | Body Mass Index |
| CBM | carbohydrate binding module |
| CI | confidence interval |
| cm | centimetre(s) |
| $C_{max}$ | maximum plasma concentration |
| CNS | central nervous system |
| COPD | chronic obstructive pulmonary disease |
| COVID-19 | coronavirus disease 2019 |
| CRF | case report form |
| CRP | C-reactive protein |
| CTA | clinical trial authorisation |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDTA | ethylenediaminetetraacetic acid |
| EU | European Union |
| $FEV_1$ | forced expiratory volume in 1 second |
| FVC | forced vital capacity |
| FSH | follicle-stimulating hormone |
| FTIH | first time in human |
| *G* | G force |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transpeptidase |
| GMP | Good Manufacturing Practice |
| GLP | Good Laboratory Practice |
| GP | General Practitioner |
| h | hour(s) |

| | |
|---|---|
| Hb | haemoglobin |
| HED | human equivalent dose |
| HIV | human immunodeficiency virus |
| HMR | Hammersmith Medicines Research |
| HRA | Health Research Authority |
| HRT | hormone replacement therapy |
| IB | investigator's brochure |
| ICH | International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IgA | immunoglobulin A |
| IgG | immunoglobulin G |
| IL-1 | interleukin-1 |
| IL-3 | interleukin-3 |
| IL-10 | interleukin-10 |
| IMP | investigational medicinal product |
| INR | international normalised ratio |
| IP-10 | interferon gamma-induced protein-10 |
| IUD | intrauterine device |
| IUS | intrauterine system |
| kD | kilo Dalton |
| kg | kilogram(s) |
| $\lambda_z$ | terminal rate constant |
| LIMS | laboratory information management system |
| LRQ | lower limit of reliable quantification |
| MABEL | minimum anticipated biological effect level |
| MCH | mean corpuscular haemoglobin |
| MCHC | mean corpuscular haemoglobin concentration |
| MCP-1 | monocyte chemoattractant protein-1 |
| MCV | mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligram(s) |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| MIA(IMP) | manufacturing authorisation for investigational medicinal products |
| MIP-1α | macrophage inflammatory protein-1α |
| µg | microgram(s) |
| µl | microlitre(s) |
| min | minute(s) |
| mL | millilitre(s) |

| | |
|---|---|
| mm | millimetre(s) |
| mm Hg | millimetres of mercury |
| MoS | margin(s) of safety |
| msec | millisecond(s) |
| NaCl | sodium chloride |
| ng | nanogram(s) |
| NOAEL | no observed adverse effect level |
| PCI | potential clinical importance |
| PCR | polymerase chain reaction |
| PD | pharmacodynamics |
| PK | pharmacokinetic(s) |
| PV | pharmacovigilance |
| QA | quality assurance |
| QC | quality control |
| QP | qualified person |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval corrected according to Fridericia's formula |
| RANTES | regulated on activation, normal T cell expressed and secreted |
| RBC | red blood cells |
| RBD | receptor binding domain |
| REC | research ethics committee |
| RES | Research Ethics Service |
| RMP | risk mitigation policy |
| RNA | ribonucleic acid |
| RSV | respiratory syncytial virus |
| RTI | respiratory tract infection |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAR | serious adverse reaction |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SOP(s) | standard operating procedure(s) |
| $SpO_2$ | peripheral arterial oxygen saturation |
| SRG | Safety Review Group |
| SSAR | suspected serious adverse reaction |
| SUSAR | suspected unexpected serious adverse reaction |
| TD | trimerisation domain |
| TEAE | treatment-emergent adverse event |
| $t_{max}$ | time of maximum plasma concentration |
| TNF-α | tumour necrosis factor-α |

| | |
|---|---|
| TOPS | The Overvolunteering Prevention System |
| UK | United Kingdom |
| ULN | upper limit of normal |
| WBC | white blood cells |

# 5 Trial personnel

| | |
|---|---|
| Principal investigator | [redacted]<br>HMR<br>Cumberland Avenue<br>London NW10 7EW<br>Tel: 020 8961 4130<br>Email: [redacted] |
| Co-investigators | [redacted]<br>HMR |
| HMR emergency contact | [redacted] |
| Statistician | [redacted]<br>HMR |
| Sponsor's representative | [redacted]<br>Pneumagen Ltd<br>Kinburn Castle, Doubledykes Road<br>St. Andrews, Fife<br>Scotland KY16 9DR<br>[redacted]<br>Email: [redacted]<br>with copy to [redacted] |
| Sponsor's medical expert | [redacted]<br>ProPharma Partners Limited<br>Tel: [redacted]<br>Email: [redacted] |
| Monitor | [redacted]<br>Ascot Research Consulting Ltd [redacted]<br>England SL5 8TE Tel: [redacted]; Mobile: [redacted]<br>Email: [redacted] |
| Laboratory safety tests | The HMR Analytical Laboratory<br>HMR |
| Demo investigational medicinal product (IMP) release testing | RSSL<br>Reading Science Centre, Whiteknights, Reading, Berkshire, RG6 6LA, UK<br>Tel: +44 (0) 118 918 4098<br>Email [redacted] |

| | |
|---|---|
| Demo IMP safety testing | Wickham Laboratories Ltd<br>Hoeford Point, Barwell Lane<br>Gosport, Hampshire<br>England PO13 0AU<br>Tel: +44 (0) 1329 226 695<br>Email: MicroAdmin@wickhamlabs.co.uk |
| Assays of IMP concentration | Alderley Analytical Ltd<br>Alderley Park<br>Macclesfield<br>Cheshire<br>SK10 4TG<br>Tel: +44 (0) 1625 238 611<br>Email [redacted] |
| Derivation of pharmacokinetic parameters | [redacted]<br>HMR |
| Pharmacovigilance | Diamond PV Services Limited<br>2, Ground Floor, Field House, Station Approach,<br>Harlow Essex, CM20 2FB, UK<br>Tel: +44 (0) 1279 406 759<br>Fax: +44 (0) 1279 418 964<br>Email: PVServices@diamondpharmaservices.com<br><br>**Serious Adverse Event reporting:**<br>**PVServices@diamondpharmaservices.com** |

# 6 Introduction

## 6.1 Background

### *6.1.1 Viral respiratory tract infections*

Viral respiratory tract infections (RTI) are of enormous global concern, particularly with the emergence of the coronavirus disease 2019 (COVID-19) pandemic (caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]). Prophylactic approaches for viral RTIs, including coronaviruses such as SARS-CoV-2, influenza, and respiratory syncytial virus (RSV), are a significant unmet need.

Vaccines are available for individual strains of influenza. However, strain coverage is not universal, and hence the risk of low vaccine effectiveness continues year on year. Furthermore, there is low efficacy of influenza vaccines in the ageing population[1,2]. Additionally, while vaccines are being rolled out against SARS-CoV-2, efficacy in the immunocompromised and immunosenescent population is not yet fully understood, and there is a significant risk of vaccine escape via viral mutations. Antivirals are also available to treat RTIs, but viral resistance remains a significant issue, and some antivirals (eg adamantanes) are no longer used for this reason. Therefore, a pan-viral prophylactic agent will complement the current prevention strategies.

### *6.1.2 COVID-19*

The global pandemic of novel COVID-19 caused by SARS-CoV-2 began in Wuhan, China, in December 2019, and has since spread worldwide. As of 09 August 2021, there have been more than 203 million reported cases and over 4 million deaths across nearly 200 countries, and the numbers are still growing.

SARS-CoV-2 likely binds to epithelial cells in the nasal cavity. From the initial infection, the virus propagates and migrates down the respiratory tract along the conducting airways. For about 80% of the infected patients, the disease will be mild and mostly restricted to the upper and conducting airways; the most common symptoms at onset of illness are fever, new unproductive cough, fatigue, myalgia and loss of taste and smell. Unfortunately, about 20% of infected patients will develop pulmonary infiltrates and typically develop dyspnoea. Some of those patients will progress to a very severe disease phenotype which can result in hospitalisation, requirement for mechanical ventilation, and substantial morbidity and mortality.

Several vaccines have now been approved for use, either by individual countries or groups of countries, such as the European Union (EU). However, it is anticipated that it will take at least another 1–2 years until most of the world's population can be vaccinated. Also, vaccination may not achieve reliable protection for elderly or immune-compromised patients who also happen to be at highest risk for unfavourable clinical course of a SARS-CoV-2 infection. Last but not least, virus

mutation may result in viral escape from vaccine-induced immunity. It is therefore anticipated that there will be an ongoing need for efficacious therapeutic agents.

### *6.1.3 Treating respiratory tract infections*

Targeting of the host glycome is a well-established mechanism for infectious diseases, including viral RTIs, to infect cells, and as such provides an avenue of strong therapeutic potential.

In the case of SARS-CoV-2, numerous studies[3,4] support a major role for the virus-surface Spike protein to facilitate cell entry by binding to host-cell angiotensin-converting enzyme 2 (ACE2) receptors. [redacted]

Human influenza viruses, such as the 2009 pandemic H1N1 virus, recognize and bind to human α-2,6–linked sialic acid receptors in the upper respiratory tract. Avian influenza viruses, such as H5N1, predominantly recognize α-2,3–linked sialic acid receptors in the human lower respiratory tract. The human H7N9 influenza virus is unusual in recognizing both types of receptors and, therefore, has the possibility of sustained human-to-human transmission and pandemic potential[7].

## 6.2 Review of investigational medicinal product

### *6.2.1 Neumifil*

[redacted]

**Figure 1: HEX17 hexavalent structure**

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

### *6.2.2 In vitro and in vivo pharmacology*

[redacted]

### 6.2.3 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 1040 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 (CNS) 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 ECG, or in diastolic and systolic blood pressure.

Standalone respiratory safety studies have not been done. 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).

### 6.2.4 Pharmacokinetics

The absorption and pharmacokinetics of Neumifil have been studied after single intravenous and intranasal doses in rats. Neumifil 0.5 mg/kg given intravenously yielded mean $C_{max}$ 1240 ng/mL, $AUC_{(0\text{-inf})}$ 2360 ng.h/mL, and terminal half-life 24.1 h (range 9.29–46.0 h). Pharmacokinetic parameters could not be calculated after intranasal administration of 4 mg/kg Neumifil, because plasma concentrations were above the lower limit of reliable quantification (LRQ: 25.0 ng/mL) in only a single sample at 2 h post dose (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 (pharmacokinetic) PK parameters, but systemic exposure was clearly minimal after repeated intranasal administration of doses up to 1040 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.

### 6.2.5 Toxicology

In the rat dose-range finding study, systemic exposure to Neumifil could not be determined because too few plasma samples had concentrations above LRQ. Rats received intranasal doses up to 1000 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 1040 µg/animal/day, but again few samples had plasma Neumifil concentrations above LRQ. The following pharmacokinetic parameters were estimated for Day 28: $C_{max}$ 123 ng/mL; $t_{max}$ 2 h; and AUC 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' 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' 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 LRQ. There were no deaths, and no effects related to the test item. 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 4 weeks' dosing was 1.65 mg/kg/day.

### 6.2.6 Pharmacodynamics

Doses of up to 100 µg *Sp*2CBMTD were administered to BALB/c mice in order 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]

[redacted]

[redacted] 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, potential pan-viral efficacy, and toxicology profile makes it suitable for progression to a FTIH study.

## 6.3 Rationale for the trial

This FTIH study will investigate the safety and tolerability of Neumifil after single and repeated intranasal administration in a randomised, double-blind, placebo-controlled trial. The results of this study will be used to select doses for subsequent trials.

## 6.4 Rationale for choice of dose(s)

### *6.4.1 Starting dose*

In the absence of the viral target, the minimum anticipated biological effect level (MABEL) is not relevant in calculating the starting dose. Instead, the safety-focused no observed adverse effect (NOAEL) approach was used.

As is typical for molecules dosed intranasally[8], the margin of safety was calculated based on both systemic and local toxicity. The Human Equivalent Dose (HED) was not corrected for body surface area, as HEX17 is a recombinant protein of molecular weight 162 kD, and proteins are typically normalised on a mg/kg basis without allometric scaling.

The NOAELs in the 28-day GLP toxicology studies in rats and Cynomolgus monkeys were 2.5 mg/kg/day and 1.65 mg/kg/day, respectively. The monkey is the more sensitive species and is also the more relevant for humans with respect to nasal structure and toxicity[9], so was used to calculate safety margins. The margins of safety for the planned first dose and maximum intended clinical dose, calculated for systemic toxicity (mg/kg/day) and local toxicity (mg/kg/cm$^2$) are shown, respectively, in Table 1 and Table 2.

**Table 1 Calculation of margins of safety for Neumifil, based on mg/kg bodyweight**

| | Monkey | Planned first clinical dose (28 µg) | Maximum intended clinical dose (885 µg) |
|---|---|---|---|
| Dose at NOAEL | 1650 µg/kg/day | n/a | n/a |
| HED (µg/kg/day; calculated for a 60 kg person) | n/a | 0.46 µg | 14.75 µg |
| MoS on µg/kg/day basis | n/a | 3587 fold | 112 fold |

HED: Human equivalent dose; MoS: Margin of Safety; NOAEL: No Observed Adverse Effect Level

**Table 2 Calculation of margins of safety for Neumifil, normalised by nasal surface area**

| | Monkey | Planned first clinical dose (28 µg) | Maximum intended clinical dose (885 µg) |
|---|---|---|---|
| Dose at NOAEL | 1650 µg/kg/day | n/a | n/a |
| HED (µg/kg/day; calculated for a 60 kg person) | n/a | 0.46 µg | 14.75 µg |
| Dose normalised by species-specific nasal surface area[1] (µg/kg/cm$^2$) | 26.78 | 0.0025 µg | 0.081 µg |
| MoS on µg/kg/cm$^2$ basis | n/a | **10,600 fold** | **331 fold** |

HED: Human equivalent dose; MoS: Margin of Safety; NOAEL: No Observed Adverse Effect Level

[1] *61.6 cm$^2$ in monkey; 181 cm$^2$ in human*

### 6.4.2 *Subsequent doses*

During the study, the dose will be escalated after review of the safety and tolerability data from previous dose level(s) by the Safety Review Group (SRG) as described in section 8.5.1.

Based on data from mice, the expected therapeutic range in humans is in the order of 0.35 mg to 3.5 mg. The doses planned in Part A have been selected to span the therapeutic range.

The doses to be tested in Part B will be selected by the SRG as describe in section 8.5.1.

The top dose will not exceed 2.8 mg

## 6.5 Assessment and management of risk

Any safety risk to study participants is mitigated by the following considerations.

- Data from pre-clinical studies suggest that Neumifil is devoid of any significant CNS or cardiovascular effects. Although standalone respiratory safety studies have not been performed, 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 range finding studies.
- In the pivotal GLP 28-day repeated dose toxicity study in rats, significant weight loss was observed in animals at the two highest dose levels: 780 and 1040 µg/animal/day (6% in male and 7% in female animals). This adverse effect was found to be reversible after 2 weeks recovery.
- Abnormal respiratory sounds (loud breathing and/or respiratory crackles) were observed at all doses levels, and this ceased after dosing was stopped.
- Mild to moderate inflammatory and reactive changes were found in the nasal mucosa and respiratory tissues, in animals receiving the two highest dose levels of Neumifil, although animals fully recovered after 2 weeks. The NOAEL in rats following 4 weeks of dosing was 2.5 mg/kg/day.
- The available pre-clinical toxicity data indicate an acceptable safety profile for Neumifil. The NOAEL in the Cynomolgus monkey corresponds to a HED of 0.46 µg in humans with a body weight of 60 kg. The proposed starting dose in Part A of 0.028 mg provides a 3587 fold and 10,600 fold margin of safety based on bodyweight or when normalised by nasal surface area respectively. The maximum selected dose provides a 112 and 331 fold margin of safety when calculated according to bodyweight, or when normalised by nasal surface area, respectively. In addition, the starting dose selected for Group B1 in Part B (multiple ascending dose part of the study) will be no higher than the highest dose that caused no safety concerns in Part A.
- Dose escalation will take place only after safety and tolerability data from preceding dose level(s) have been reviewed. There will be an appropriate interval between sequential groups, to allow for review of those data. Dose escalation will be halted if the stopping criteria are met (see section 8.4.2).
- As Neumifil has never been given to humans before, each new ascending dose will be staggered: sentinel subject will be dosed first, and the remaining subjects will be dosed at least 23 h later.
- If the dose level selected is no higher than one that has already been shown to cause no safety concerns, sentinel subjects will not be required, and subjects will be dosed at intervals of at least 10 min. The maximum dose will not exceed 2.8 mg.
- As this is a first-in-human study, the investigator must obtain a reply from the GP, or have a valid GP reply on file, before dosing a subject (Part A).

- Only subjects who are identified as healthy in respect of major organ classes, as assessed by their medical history, and clinical and laboratory variables will be included in the study.
- Subjects with presence or history of respiratory disease will be excluded from the study. Respiratory function will also be assessed in the form of spirometry at screening.
- Subjects will be monitored frequently throughout the study for safety and tolerability. The safety monitoring practices employed by this protocol are adequate to protect the subjects' safety and should detect all expected treatment emergent adverse events (TEAEs).
- HMR is accredited by the Medicines and Healthcare products Regulatory Agency (MHRA) to do first-in-human studies and will follow its standard operating procedures (SOPs).
- HMR maintains its own resuscitation team (SOP SS329) to deal with medical emergencies, including anaphylaxis and cardiac arrest. The team will be on duty continuously, until at least 24 h after each dose.
- Any risks are adequately mitigated by safety assessments, and by the medical cover provided by the investigator site, and by appropriate IMP manufacture, according to Good Manufacturing Practice (GMP).
- There will be no direct health benefit for study participants from receipt of study medication. An indirect health benefit to the healthy subjects enrolled in this trial is the free medical examination received at screening and during the study.
- The overall risk benefit balance is considered to be acceptable.

### *6.5.1 Conducting the trial during the COVID-19 pandemic*

The principal investigator and sponsor have reviewed the risks of conducting the trial in light of the current COVID-19 pandemic. The first priority is the safety of trial subjects and staff, but we also have an ethical duty to preserve the scientific integrity of the trial as far as possible.

Neumifil is a potential medication against SARS-CoV-2 infection, although this study is in healthy volunteers and no benefit is expected. Preliminary non-clinical data indicate that Neumifil can protect recipient animals (Syrian hamster) against infection by SARS-CoV-2 and therefore no specific risks to participants due to conducting the study during the COVID-19 pandemic are anticipated. Non-clinical work in mice, has shown that pre-treatment of mice with Neumifil, before a lethal influenza challenge, protects mice from the viral challenge and does not reduce the development of protective immune responses against the influenza strain. Therefore, it is not anticipated that Neumifil will attenuate the immune response to a vaccine. No interaction between Neumifil and vaccinations against COVID-19 are anticipated.

The purpose of this study is to assess safety and tolerability of Neumifil; to avoid an overlap of adverse events, the administration of Neumifil will not be within 7 days of

a vaccination against COVID-19. Subjects will be resident in the HMR Phase 1 unit for the dosing period. Avoiding administering Neumifil within 7 days of a COVID-19 vaccination will mean subjects in Part A will have a 14-day window (Day –7 to Day 8 with dosing on Day 1) when they will not be eligible for the study if they have a COVID-19 vaccination booked. In Part B there will be a 21-day window (Day –7 to Day 15 with dosing on Day 1) when they will not be eligible for the study if they have a COVID-19 vaccination booked.

This clinical trial will be done in accordance with HMR's COVID-19 risk mitigation policy (RMP), which documents HMR's COVID-19 virus testing strategy for volunteers and staff, social distancing measures, and management of COVID-19-like symptoms. HMR's RMP was first notified to the MHRA and Health Research Authority (HRA) on 22 May 2020, and applies across all HMR's trials. The mitigation measures specified in the HMR COVID-19 RMP are deemed adequate for this trial. Any deviations from the RMP will be documented in a separate COVID-19 trial-specific risk assessment, prepared by the investigator. Any deviations from the protocol that result from the COVID-19 pandemic, and COVID-19 related AEs or SAEs, will be documented.

Taking the above factors into account, and the proposed mitigation, we believe that it is medically and ethically acceptable to proceed with the trial during the current COVID-19 pandemic.

# 7 Objectives and endpoints

## 7.1 Objectives

### *7.1.1 Primary objectives*

*Part A*

- To assess the safety and tolerability of single-ascending intranasal doses of Neumifil in healthy subjects.

*Part B*

- To assess the safety and tolerability of multiple-ascending intranasal doses of Neumifil in healthy subjects.

### *7.1.2 Exploratory objective*

- To determine the number of subjects contracting SARS-CoV-2 during the 7 days after receiving their (last) dose.
- To assess the formation of Neumifil ADAs after multiple-ascending intranasal doses in healthy subjects (Part B only).

- To assess the plasma concentration of single- or multiple-ascending intranasal doses of Neumifil in healthy subjects to determine if intranasal administration results in systemic exposure.
- To assess the concentrations of cytokines and chemokines in nasal secretions before dosing and after multiple intranasal doses of Neumifil (Part B only).

## 7.2 Endpoints

### *7.2.1 Primary endpoints*

*Safety and tolerability:*

Clinically significant changes in: vital signs (heart rate, blood pressure, respiratory rate, pulse oximetry and temperature), 12-lead ECG, $FEV_1$, FVC, physical examination, nasal examination, laboratory safety tests (haematology, biochemistry and urinalysis), tolerability questionnaire, AEs and serious AEs (SAEs). Safety endpoints will be assessed up to 7 days after dosing in Part A or up to 14 days after the last dose in Part B.

### *7.2.2 Exploratory endpoint*

*Safety:* SARS-CoV-2 infection test, done at screening, before the first dose, on Day 8 (Part B only), and at follow-up.

*Immunogenicity:* ADAs of Neumifil, as assessed by IgA and IgG concentration, derived from blood samples taken before the first dose and at Follow-up (Part B only).

*Plasma concentration of Neumifil:* Plasma concentrations of Neumifil after single doses on Day 1 in Part A, and after dosing on Days 1 and 7 in Part B.

*Cytokine and chemokine concentrations in nasal secretions:* Presence and concentration of cytokines and chemokines, measured by multiplex assay, in nasal wick samples collected on Day –1, Day 8, and at follow up (Part B only).

# 8 Overall trial design

## 8.1 Trial design

This is a Phase 1, single-centre, randomised, placebo-controlled FTIH study in healthy subjects. The study is in 2 parts and will investigate single-ascending (Part A) and multiple-ascending (Part B) doses of Neumifil, administered intranasally.

Schematic diagrams of the study design are in section 8.2.

### *8.1.1 Part A*

Enrolment of up to 36 healthy subjects is planned, in up to 5 groups (Groups A1−A5). Groups A1–A3 will consist of 6 subjects each, and Groups A4 and A5 will consist of 9 subjects each.

Subjects will receive a single intranasal dose of Neumifil or placebo. In Groups A1−A3, 4 subjects will receive Neumifil and 2 will receive matching placebo. In Groups A4 and A5, 6 subjects will receive Neumifil and 3 will receive matching placebo. Additional dose levels may be explored in up to 2 optional groups of up to 9 subjects each.

The starting dose for Group A1 is 0.028 mg Neumifil. Subsequent planned doses are given in Table 3.

**Table 3 Planned doses in Part A**

| Group | Planned nominal dose of Neumifil | Number of subjects | Number on placebo |
|---|---|---|---|
| A1 | 0.028 mg | 6 | 2 |
| A2 | 0.085 mg | 6 | 2 |
| A3 | 0.28 mg | 6 | 2 |
| A4 | 0.885 mg | 9 | 3 |
| A5 | 2.8 mg | 9 | 3 |
| A6 (optional) | To be decided | 9 | 3 |
| A7 (optional) | To be decided | 9 | 3 |

Because Neumifil has never been given to humans before, each new ascending dose will be staggered: sentinel subjects will be dosed first, and the remaining subjects will be dosed at least 23 h later. To maintain the blind nature of the study, the 2 sentinel subjects will be randomised to ensure that 1 subject receives active treatment and the other receives placebo. Since 1 subject will receive placebo treatment, the sentinel subjects may be dosed at least 5 min apart. Provided the investigator considers the safety and tolerability in the sentinel subjects to have been acceptable, the remaining subjects will be dosed, at intervals of at least 10 min.

The planned dose levels may be changed, depending on the safety and tolerability results after previous doses, as described in section 8.5. The dose will not be escalated unless the safety and tolerability of the previous dose is acceptable. There will be an appropriate interval between sequential groups, to allow for review of those data. If the dose level selected is no higher than one that has already been shown to cause no safety concerns, sentinel subjects will not be required, and subjects will be dosed at intervals of at least 10 min. The maximum dose will not exceed 2.8 mg.

Subjects will be screened within 35 days before their dose of trial medication. Subjects will be resident on ward from 1 day before their dose (Day –1) until about 24 h after dosing (Day 2). They will return for a follow-up visit 7–8 days after their dose (Day 8–9).

### *8.1.2 Part B*

Enrolment of up to 24 healthy subjects is planned, in up to 3 groups of 8 subjects (Groups B1−B3).

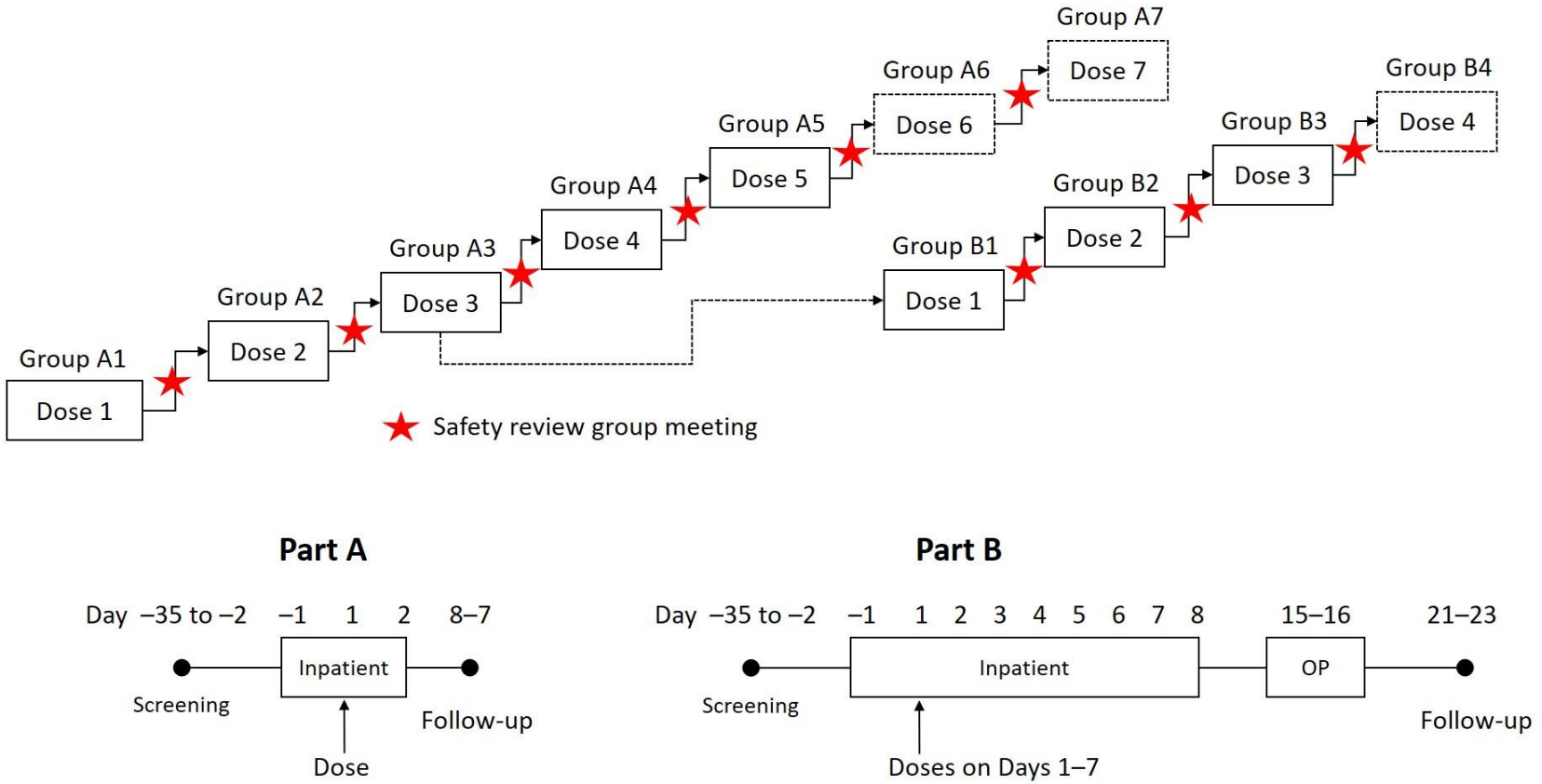
Subjects will receive once-daily intranasal doses of Neumifil or placebo for 7 days. In each group, 6 subjects will receive Neumifil and 2 will receive matching placebo.

Part B can start before completion of Part A. The starting dose level (dose and dose regimen) for Group B1 will be decided after review of safety and tolerability data from at least 3 dose levels in Part A, and will be no higher than a dose that has previously been shown to cause no safety concerns in Part A (see section 8.5.3). An additional dose level may be explored in 1 optional group of up to 8 subjects (Group B4). Subsequent doses levels, including maximum duration of dosing, will be determined as described in Part A.

Subjects will be screened within 35 days before their dose of trial medication. Subjects will be resident on ward from 1 day before their dose (Day –1) until about 24 h after their last dose (Day 8). Subjects will attend an outpatient visit at 7−8 days after their last dose (Days 15–16). They will then return for a follow-up visit at 13−15 days after their dose (Days 21–23).

## 8.2 Study flow chart

### Figure 3 Study flow chart




OP: outpatient visit. Part B can start after review of safety and tolerability data from at least 3 dose levels in Part A. Groups A6, A7 and B4 are optional. Dose selection for Part A and B is described in section 8.5.2 and 8.5.3.

## 8.3 Definition of the end of the trial

The end of the trial is defined as the final follow-up visit by the last subject. If the trial is terminated prematurely, the trial ends when the sponsor notifies the investigator in writing that the trial has finished, or when the last subject attends the final follow-up visit, whichever is later.

## 8.4 Stopping criteria

### *8.4.1 Trial stopping criteria*

The trial will be stopped if either of the following occurs:

- one or more SAEs considered to be at least possibly related to study treatment; or
- 2 or more severe or clinically significant AEs considered to be at least possibly related to study treatment at any dose level.

Treatment allocations may be unblinded to aid safety review, provided that the unblinding is appropriately documented.

If, after an internal safety review, it is appropriate to restart the trial, a substantial amendment will be submitted to the MHRA and research ethics committee (REC). The trial will not restart until the amendment has been approved by the MHRA and REC.

### *8.4.2 Dose escalation stopping criteria*

A dose level will not be repeated, or exceeded, if either of the following apply:

- the results of safety tests give the sponsor or investigator cause for concern
- the investigator or sponsor considers that dose level to be poorly tolerated

The trial will be stopped if any criterion in section 8.4.1 is met.

See section 9.4 for individual subject withdrawal criteria. Dosing will be discontinued in an individual if any criterion in section 9.4 is met.

## 8.5 Criteria for dose selection

### *8.5.1 Review of data by the SRG*

During the study, the dose level (dose and [if applicable] dose regimen) will be increased only if the safety and tolerability of the previous dose level is acceptable.

All dose levels will be selected by the SRG, which will include (as a minimum) the principal investigator (or delegate) and the sponsor's medically qualified

representative (or delegate). Each dose decision will be made and documented in line with HMR SOPs.

Before confirming the dose level for any group, the SRG will review, as a minimum, safety and tolerability data from the previous dose level and (if different) the highest dose level tested to date, as described below. Safety and tolerability data obtained from the previous group(s) will also be reviewed, if applicable. All data used to support dose selection will be quality checked.

*Review of safety and tolerability data*

The SRG will review (as a minimum) safety and tolerability data, up to 7 days after (final) dosing, from at least 4 evaluable subjects who have received active treatment at the highest dose level tested to date. An evaluable subject is one who completes dosing, has undergone procedures until 7 days after (final) dosing, and has no major protocol deviations. To maintain blinding, data from at least 6 subjects in each group of 6 (Groups A1–A3) or 8 (Groups B1–B3), or from at least 7 subjects in each group of 9 (Groups A4 and A5), must be reviewed to ensure that the dataset includes at least 4 evaluable subjects on active treatment. If fewer subjects than planned are dosed, any subjects required to complete the group may be dosed in parallel with subsequent groups.

The safety data reviewed will include, as a minimum:

- AEs and SAEs, including description, intensity, onset, duration, and relationship to treatment
- vital signs
- 12-lead safety ECG
- laboratory safety tests
- physical examination
- nasal examination
- $FEV_1$
- tolerability questionnaire

*Review of pharmacokinetic data*

It is not expected that a review of the PK will form part of the dose escalation decision, as the plasma concentrations are expected to be very low/not detectable. However, if PK data are reviewed, dummy-subject identifiers will be applied to the data by the bioanalytical laboratory, or an unblinded programmer at HMR, so that individual data may be reviewed without unblinding the investigator or any blinded sponsor representatives. If fewer subjects are dosed than planned, to avoid potential unblinding, individual data will not be reviewed – mean, minimum and maximum data will be reviewed, and number of subjects will not be presented. If there are missing PK data at a particular timepoint, the missing data may be replaced by an interpolated value to maintain blinding.

### 8.5.2 Dose selection for Part A

Planned dose levels in Part A (Table 3) may be changed based on emerging data.

It is expected that the dose level will be increased for each group (Groups A1–A5). The dose will be increased such that it does not exceed 3.5-times the highest dose level that was safe and well tolerated.

Two further dose levels may be explored in the optional groups of subjects (Groups A6 and A7). No dose will exceed 2.8 mg. The trial will be stopped if the criteria in section 8.4.1 are met.

The scheduled dose of Neumifil may be reduced if, for example, the results of safety tests give us cause for concern, or tolerability is poor.

### 8.5.3 Dose selection for Part B

Part B will not proceed until the SRG has reviewed safety and tolerability data (up to 7 days after dosing) from at least 3 dose levels in Part A, as described in section 8.5.1.

The first total daily dose level (dose and dose regimen [ie once- or twice-daily]) to be tested in in Part B will be the same as, or lower than the highest single dose level that has been given in Part A without any safety concerns. For subsequent groups in Part B, the dose level will be escalated only if the safety and tolerability of the previous dose level are acceptable and do not exceed the highest single dose tested in Part A that caused no safety concerns.

The planned duration of dosing (7 days) may be changed based on emerging data but will not exceed 14 days.

### 8.5.4 Repeating a dose level or selection of a lower dose level (Parts A and B)

In Parts A and B, it is expected that the dose will be increased for each group.

The SRG may decide to test a lower dose level of Neumifil, or to repeat a dose level, provided it does not meet any of the criteria in Section 8.4. Such decisions will be made and documented in line with HMR SOPs. A dose level may be repeated under the following circumstances.

- If it was safe and well tolerated.
- If AEs occur that cause mild or moderate discomfort, but do not in any way threaten the health of the subject, that dose level may be repeated with the aim of exploring further the relationship between dose and AE. If, in the SRG's judgement, it would be unreasonable to expose further subjects to the level of discomfort experienced by the subjects who have already received the dose, a lower dose may be tested. The selected dose will be either a lower dose level that has already been given, or an intermediate level that has not previously been

given; in either case, the aim is to learn more about the relationship between AEs and dose of Neumifil.

# 9 Trial population

## 9.1 Planned number of subjects

Up to 60 healthy volunteers (up to 36 in Part A and up to 24 in Part B), excluding replacements and optional groups.

## 9.2 Inclusion criteria

1. Healthy male or female volunteer, aged 18–60 years.
2. BMI (Quetelet index) in the range 18.0–30.9 kg/m$^2$.

$$\text{Body Mass Index} = \frac{\text{weight [kg]}}{(\text{height [m]})^2}$$

3. Able to understand the nature of the trial and any hazards of participating in it. Ability to communicate satisfactorily with the investigator and to participate in, and comply with the requirements of, the entire trial.
4. Willingness to give written consent to participate after reading the information and consent form, and after having the opportunity to discuss the trial with the investigator or their delegate.
5. Agree to follow the contraception requirements of the trial as described in section 11.
6. Agree not to donate blood or blood products during the study and for up to 3 months after the administration of the trial medication.
7. Spirometry readings ($FEV_1$ and FVC) to be ≥ 80% of predicted value at the screening visit, calculated using National Health and Nutrition Examination Survey (NHANES) reference. If a subject's $FEV_1$ or FVC is outside that range at the screening visit, the test may be repeated once on another day.
8. Registered with a General Practitioner (GP) in the UK (Part A only).
9. Willingness to give written consent to have data entered into The Overvolunteering Prevention System (TOPS).

## 9.3 Exclusion criteria

1. Woman who is pregnant or lactating, or pre-menopausal woman who is sexually active and not using a reliable method of contraception (see section 11).
2. Clinically relevant abnormal medical history, physical findings, ECG, or laboratory values at the pre-trial screening assessment that in the opinion of the

investigator could interfere with the objectives of the trial or the safety of the volunteer.

3. Presence or history of acute or chronic illness sufficient to invalidate the volunteer's participation in the trial or make it unnecessarily hazardous.
4. Presence or history of respiratory disease, including (but not limited to) asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, emphysema, requiring acute or chronic medication.
5. Presence of nasal polyps or significant nasal abnormalities.
6. Symptoms of respiratory illness (including, but not limited to, runny nose, sore throat, sneezing, coughing or wheezing) at the screening visit or before dosing on Day 1.
7. Tympanic temperature > 37.5°C at the screening visit or before dosing on Day 1.
8. Impaired endocrine, thyroid, hepatic, respiratory or renal function, diabetes mellitus, coronary heart disease, or history of any psychotic mental illness.
9. History of psychiatric disease, as determine by the investigator.
10. History or presence of malignant disease.
11. Immune-suppressed status, resulting from either disease or medication, as determined by the investigator.
12. Presence or history of severe adverse reaction to any drug or the excipients of Neumifil.
13. Known allergy to tetracycline antibiotics.
14. Use of a prescription medicine (except HRT in female subjects), including oral contraceptives, during the 28 days before the first dose of trial medication, or use of an over-the-counter medicine, with the exception of acetaminophen (paracetamol) and vitamin or nutritional supplements, during the 7 days before the first dose of trial medication.
15. Receipt of an investigational product (including prescription medicines) as part of another clinical trial within the 3 months before admission to this study; in the follow-up period of another clinical trial at the time of screening for this study.
16. Receipt of a COVID-19 vaccine within 7 days before the first dose of trial medication, or anticipate receiving a COVID-19 vaccine within the 7 days after a (final) dose of trial medication.
17. Presence or history of drug or alcohol abuse, or regular intake of more than 14 units of alcohol weekly.
18. Use of cigarettes or nicotine-containing products during the 6 months before first dose of trial medication.

19. Blood pressure and heart rate in supine position at the screening examination outside the ranges: blood pressure 90–140 mm Hg systolic, 40–90 mm Hg diastolic; heart rate 40–100 beats/min. Triplicate measurements will be made (at least 2 min apart), and a mean value outside the above ranges will lead to exclusion.

    Repeat measurements (in triplicate) are permitted if values are borderline (ie values that are within 5 mm Hg for blood pressure or 5 beats/min for heart rate) or if requested by the investigator. Subjects can be included if the repeat value is within range or still borderline but deemed not clinically significant by the investigator.

20. QTcF value, of > 450 msec (men) or > 470 msec (women); or QRS duration ≥ 120 msec, measured on 12-lead ECG at the screening visit. Triplicate measurements will be made, and a mean value used to determine eligibility. A repeat (in triplicate) is also allowed on one occasion for determination of eligibility.
21. Possibility that the volunteer will not cooperate with the requirements of the protocol.
22. Positive test for hepatitis B surface antigen, hepatitis C or HIV. NOTE: participants with positive hepatitis C antibody owing to resolved disease can be included only if a hepatitis C ribonucleic acid (RNA) test is negative.
23. Positive test for SARS-CoV-2 (polymerase chain reaction; PCR) or suspected exposure to the SARS-CoV-19 virus during the 14 days before screening.
24. Loss of more than 400 mL blood during the 3 months before the trial, eg as a blood donor.
25. Objection by GP to volunteer entering trial.

## 9.4 Withdrawal of subjects from the trial

### *9.4.1 Withdrawal of subjects*

Subjects are free to withdraw from the trial at any time without giving reasons. Furthermore, the investigator may withdraw a subject for reasons such as intolerance to trial medication, intercurrent illness, need for medication, which is contraindicated, significant non-compliance with the requirements of the trial, or withdrawal of consent. The investigator will assess the reasons for withdrawal as far as possible and will fully record the circumstances and medical details.

### *9.4.2 Individual subject stopping criteria (Part B only)*

A subject who meets any of the following criteria will receive no further doses.

- SAE considered related to study treatment.

- alanine aminotransferase (ALT) ≥ 5 x the upper limit of normal (ULN).
- ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN or international normalised ratio (INR) of ≥1.5, as per the guidelines for acute liver failure (if a subject meets that withdrawal criterion, serum bilirubin fractionation should be performed).
- ALT ≥ 3 x ULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia). Subjects who have ALT ≥ 3 x ULN and < 5 x ULN, and total bilirubin < 2 x ULN, who do not exhibit hepatitis symptoms or rash, can continue in the study (and continue receiving trial medication) as long as they can be monitored weekly until liver chemistries return to within baseline values.
- $FEV_1$ or FVC of < 80% predicted or a decrease of > 20% from baseline
- Peripheral arterial oxygen saturation ($SpO_2$) of < 94%

Subjects who meet the above criteria will be considered discontinued from dosing. However, the investigator may ask the subject to continue their participation in the study so they can be monitored for safety, PK and immunogenicity, or the investigator may withdraw the subject from the trial.

Subjects will be informed before they agree to take part in the trial that, if they withdraw or are withdrawn:

- the investigator will stop collecting information about them; and
- they can ask the investigator to destroy any identifiable samples taken from them.

The investigator will ask withdrawn subjects to provide written consent to a follow-up examination, to check that they have come to no harm as a result of taking part in the trial. Provided that the subject agrees, they will undergo, at withdrawal from the trial (or as soon as possible afterwards), the standard medical examination and laboratory tests which they would have undergone had they completed it. The investigator will record in the case report form (CRF) the results of the follow-up examination of withdrawn subjects, if they give their consent for that.

### *9.4.3 Replacement of withdrawn subjects*

Withdrawn subjects will be replaced at the discretion of the sponsor and investigator. Replacements for withdrawn subjects will receive the treatment(s) intended for the withdrawn subject.

# 10 Treatments

## 10.1 Treatments administered

Part A: subjects will receive a single dose of Neumifil or placebo.

Part B: subjects will receive once-daily doses of Neumifil or placebo for 7 days.

All doses will be administered intranasally using an Aptar liquid delivery system. Each dose will consist of nasal drops/spray administered as a maximum volume of 0.5 mL to each nostril. Subjects must lie supine for 5 min after dosing. Further details will be provided in a separate manual.

Fasting requirements are described in section 11.

## 10.2 Overdose

Symptoms of overdose of Neumifil are not yet known. In the case of accidental overdose, subjects should be treated symptomatically as no specific antidote is available.

## 10.3 Blinding

The trial medication will be repackaged and relabelled by the HMR Pharmacy, according to the randomisation schedule. Active and placebo treatments will be labelled such that it is not possible to distinguish between them. If the expiry dates of placebo and active treatment differ, both treatments will be labelled with an expiry date no later than the earlier of the 2 expiry dates. Each subject's treatment will be given a unique code number, traceable to the batch number of the medication.

The placebo and active treatments for each group will be identical in appearance, and similar in taste and smell. To maintain the blind nature of the trial, in each group, the number of sprays of placebo treatment will be the same as active treatment.

A sealed copy of the randomisation code will be kept in a locked file in the HMR Pharmacy. A copy will also be kept by the bioanalytical laboratory. The investigator will be supplied with sealed envelopes, each one containing the treatment allocation for the subject whose number appears on the outside of the envelope. Those envelopes will be kept in the trial master file, readily accessible to clinical staff. Sealed individual code break envelopes will also be provided to the Pharmacovigilance Service Provider. Emergency procedures for revealing medication codes are specified in section 10.4.

The investigators, medical monitor and clinical monitor will remain blinded throughout the trial, unless safety concerns necessitate unblinding (see section 10.4 below).

## 10.4 Unblinding procedure

If unblinding is required in the interest of the safety of a subject (for example, in a medical emergency where the identity of the investigational material will affect the management of the subject), the principal investigator or delegate will open the individual code-break envelope for that subject without prior consultation with the

sponsor. In that event, the principal investigator or delegate will notify the sponsor as soon as possible (within 24 h) that the randomisation code has been broken for the subject. If unblinding may be helpful, but is not required immediately (for example, the information may be useful to make decisions for other subjects in the group), wherever possible, an investigator will discuss the matter with the sponsor before opening any individual code-break envelopes.

When the trial database for the relevant study part has been locked, the HMR statistician will inform the sponsor of his or her intention to break the randomisation code. The statistician will break the code, and do the statistical analysis of the relevant data.

## 10.5 Method of assigning subjects to treatment groups

Volunteers will be assigned a unique screening number, from 001 onward, at their screening visit. After passing all of the screening assessments, subjects will be allocated to study part and group, as described below, according to their availability and the scheduled trial dates.

Subjects will be numbered consecutively, in the order in which they arrive on the ward and are entered into the trial. Subject numbers are presented in Table 4. Subject numbers will be allocated to treatments (active or placebo) according to a randomisation schedule prepared by an independent HMR statistician, using a SAS program.

Subject numbers, and sentinel subject numbers for Part A, are provided in Table 4; at each dose level, subjects will receive active or placebo treatment as described in section 8.1.

Randomisation is described further in section 8.1.

**Table 4 Subject and sentinel numbers**

| Study part | Group | Subject numbers | Sentinel subjects |
|---|---|---|---|
| A | A1 | 1001–1006 | 1001 and 1002 |
| | A2 | 1007–1012 | 1007 and 1008 |
| | A3 | 1013–1018 | 1013 and 1014 |
| | A4 | 1019–1027 | 1019 and 1020 |
| | A5 | 1028–1036 | 1028 and 1029 |
| | A6* | 1037–1045 | 1037 and 1038 |
| | A7* | 1046–1054 | 1046 and 1047 |
| B | B1 | 2001–2008 | – |
| | B2 | 2009–2016 | – |
| | B3 | 2017–2024 | – |
| | B4* | 2025–2032 | – |

* optional groups.

Replacements for withdrawn subjects will be given a number equal to that of the subject that they replaced plus 100. So, Subject 1001 would be replaced by Subject 1101, and Subject 2025 would be replaced by Subject 2125, and so on.

### 10.6 Selection and timing of dose for each subject

The treatments to be administered are described in sections 8.1 and 10.1. Subjects will be randomly assigned to those treatments, as described in section 10.5 above.

Because Neumifil has never been given to humans before, each new ascending dose in Part A will be staggered as described in section 8.1.

In Part A, all doses will be given in the morning. In Part B, doses will be given once or twice-daily at the same time each day (± 15 mins from the time of dosing on Day 1).

### 10.7 Previous and concomitant treatment

Restrictions on previous medication are described in exclusion criterion 14.

During the trial, concomitant medication may be given if the subject's GP believes it to be necessary. In addition, up to 4 doses of 500 mg paracetamol will be allowed per day for mild analgesia. No COVID-19 vaccine is allowed during the 7 days before the first dose of trial medication or the 7 days after the final dose of trial medication. Any other concomitant treatment will be given only if deemed strictly necessary by the investigator or co-investigator. In any case, all concomitant treatments will be reported in the CRF along with their daily dosage, duration, route of administration, and reasons for administration. Subjects who have received any concomitant treatment may be withdrawn from the trial at the discretion of an investigator.

### 10.8 Assessment of compliance

Subjects will be dosed on the research ward under the supervision of 2 suitably trained members of HMR staff.

## 11 Dietary and lifestyle restrictions

Subjects will abide by HMR house rules while on the ward.

*Part A*

Subjects will fast (no food or drink other than water) overnight for ≥ 8 h before dosing until 2 h after dosing on Day 1. Standard meals will be provided at about 2, 4 and 10 h after dosing.

*Part B*

*Morning dose:* Subjects will fast (no food or drink other than water) overnight for ≥ 8 h before dosing until 2 h after dosing on Day 1 and Day 7. Standard meals will be provided at about 2, 4 and 10 h after dosing on Day 1 and Day 7.

*Evening dose (if applicable)*: Subjects will fast (no food or drink other than water) for at least 2 h before and 2 h after dosing on Day 1 and 7.

At all other times during the study, standard meals will be given at usual times.

*All study parts*

During the study, subjects will fast for at least 8 h before laboratory safety blood samples are taken at screening, on admission (Day –1), and Follow-up.

No alcoholic drinks or smoking will be allowed during the period from 24 h before admission until follow-up. No caffeinated drinks will be allowed from 24 h before admission until discharge from the ward (Day 2 in Part A and Day 8 in Part B). No strenuous exercise will be allowed from 2 days before screening until follow-up.

Subjects will rest in bed in the supine position during and until ≥ 5 min after dosing.

Subjects must not sunbathe or use a sunbed during the study.

Subjects must use a reliable method of contraception[10], as follows.

***Men***

Male subjects must not plan to father a child, or donate sperm, from dosing until 3 months after their (last) dose.

Male subjects must not have sex without using a condom, from dosing until 3 months after their (last) dose, if their partner is a woman of childbearing potential. They do not need to use any contraception if: they've had a vasectomy, and surgical success has been confirmed by medical assessment; their partner has had a bilateral tubal ligation; or their partner is not of childbearing potential. Partners who are not of childbearing potential are defined as: men; post-menopausal women (no menstrual periods for at least 12 months); or women who have no uterus, ovaries or fallopian tubes.

***Women***

Women of childbearing potential must use a highly effective method of contraception with low-user dependency during the trial, and for up to one month after the final follow up visit. They must have been using that method for at least 28 days before the start of the trial. Highly effective methods of contraception include:

- Progestogen-only hormonal contraception implants associated with inhibition of ovulation
- Intrauterine device (IUD)

- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion or ligation
- Vasectomised partner (with surgical success confirmed by medical assessment)

A woman is considered to be of non-childbearing potential if she meets one of the following criteria:

- is post-menopausal (the last menstrual period was at least 12 months ago, and Follicle Stimulating Hormone (FSH) test at screening confirms post-menopausal status)
- has no uterus, ovaries or fallopian tubes

Women who are taking HRT must use contraception (as described above) during the trial unless prescribed following bilateral oophorectomy, hysterectomy or salpingectomy.

Combined or progesterone-only hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal or injections) are not allowed.

Subjects who practise true abstinence or who only have same-sex relationships need not use contraception, provided it is in line with their preferred and usual lifestyle (note: periodic abstinence [eg calendar, ovulation, symptothermal, and post-ovulation methods] and withdrawal are not acceptable methods of contraception). Should any such subject stop practising true abstinence, they must use contraception as described above.

# 12 Procedures and observations

Only subjects who meet all the inclusion and no exclusion criteria will be eligible for enrolment into the trial (see section 9). Each subject will be allocated a unique trial number (see section 10.5).

Additional time points may be introduced, and changes to time points may be made, in accordance with section 12.2.

The following assessments will be made at the timepoints given in in sections 12.1.1 (Part A) and 12.1.2 (Part B).

*Safety and tolerability*

Laboratory assessments (haematology, biochemistry and urinalysis), physical examinations, 12-lead ECGs, vital signs (heart rate, blood pressure, respiratory rate, pulse oximetry and temperature), nasal examinations and spirometry will be done before and during dosing and frequently until the subject's last visit in each study part. Subjects will complete a tolerability questionnaire post-dose after each dose of Neumifil. AEs will be recorded from screening until the subject's last visit in each study part.

The schedules of procedures are in sections 12.1.1 (Part A) and 12.1.2 (Part B). Laboratory safety variables to be assessed during the study are in Table 7.

Throughout the study, AEs and concomitant medication will be documented as they are reported by the subjects. Subjects will be questioned about AEs when procedures are done, and when they return to the ward for outpatient visits (Part B only), and at follow-up.

*Plasma concentration of Neumifil*

Blood samples for assay of Neumifil will be taken before and up to 3 h after dosing on Day 1 (Part A) and Days 1 and 7 (Part B).

*Immunogenicity*

Blood samples for assay of Neumifil ADAs will be taken before dosing on Day 1 and on Day 22 (Part B only).

## 12.1 Schedule of procedures

### *12.1.1 Part A*

| Period: | Screening [1] | | Study session | | | | | | | | | | | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Day:* | *–35 to –2* | *–1* | | *1* | | | | | | | | | | *2* | *8 to 9* |
| *Time (h)* | | | *Pre* | *0* | *0.25* | *0.5* | *1* | *2* | *2.5* | *3* | *4* | *8* | *12* | *24* | |
| Informed consent | X | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | X | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | |
| Admission | | X | | | | | | | | | | | | | |
| Inpatient stay | | ◄ | | | | | | | | | | | ► | | |
| Discharge | | | | | | | | | | | | | | X | |
| Safety assessments | | | | | | | | | | | | | | | |
| Physical examination[2] | X | X | | | | | X | | | | | | | X | X |
| Height & weight[3] | X | X | | | | | | | | | | | | | X |
| Vital signs[4] | X | X | X | | | | | X | | | X | X | X | X | X |
| 12-lead ECG[5] | X | | X | | | | | | X | | | | | | X |
| Serology | X | | | | | | | | | | | | | | |
| Laboratory safety tests[6] | X | X | X | | | | | | | | | X | | X | X |
| Pregnancy[7] | X | X | | | | | | | | | | | | | X |
| FSH[8] | X | | | | | | | | | | | | | | |
| Urine drug, alcohol and cotinine tests | X | X | | | | | | | | | | | | | |
| Spirometry[9] | X | | | | | | | | | | X | X | X | X | X |
| Nasal examination | X | X | | | | | | | | | | | | X | X |
| SARS-CoV-2 infection test[10] | X | X | | | | | | | | | | | | | X |
| Self-assessment nasal tolerability rating scale | | | | | | | X | | | | | | X | | |
| Dosing | | | | | | | | | | | | | | | |
| Intranasal Neumifil | | | | X | | | | | | | | | | | |
| Neumifil PK | | | | | | | | | | | | | | | |
| PK sampling[11] | | | X | | | | X | X | | X | | | | | |

| | |
|---|---|
| Ongoing subject review | |
| Concomitant medicines | ◄——— |
| AEs | ◄——— |

Abbreviations: ECG: electrocardiogram; FSH: follicle-stimulating hormone; PK: pharmacokinetics; AEs: adverse events.

**Notes:**

1. Screening will be within 35 days before dosing
2. Full physical examinations will be done at screening and on Day –1. Brief (symptom-directed) physical examinations will be done at all other timepoints.
3. Height measured at screening only.
4. Vital signs consist of: systolic and diastolic blood pressure, heart rate, pulse oximetry, temperature and respiratory rate. They will be assessed at screening; on Day –1, and before and at 2, 4, 8, 12 and 24 h after dosing on Day 1; and at follow-up. Triplicate measurements (at least 2 min apart) will be made at screening and before dosing. Single measurements will be made at all other time points. Measurements should be made with subjects in a supine position, after resting for 5 min.
5. ECGs will be recorded at screening; before and at 2.5 h after dosing on Day 1; and at follow-up. Triplicate recordings (at least 2 min apart) will be made at screening and before dosing; single recordings will be done at all other time points. Recordings should be made with subjects in a supine position, after resting for 5 min.
6. Laboratory safety tests consist of biochemistry, haematology and urinalysis in serum. They will be done at screening; on Day –1, and before and at 8 and 24 h after dosing on Day 1; and at follow-up. Subjects should fast for ≥ 8 h before laboratory safety tests at screening, admission (Day –1), and follow-up.
7. Pregnancy tests in women of child-bearing potential only.
8. FSH tests in post-menopausal women at screening only.
9. $FEV_1$ and FVC will be measured at screening; at 4, 8, 12 and 24 after dosing on Day 1; and at follow-up.
10. If a subject develops symptoms of COVID-19, ad hoc SARS-CoV-2 infection tests will be done.
11. Blood samples for assay of Neumifil will be taken before and at 1, 2, and 3 h after dosing on Day 1.

When more than one procedure is scheduled at a specific time point, procedures should be done in the following order: ECG, vital signs, blood samples (at the scheduled time), then spirometry. Blood sampling should be done on time. Other procedures should be done as close as possible to the scheduled time point.

### 12.1.2 Part B

| Period: | Screening[1] | Study session | | | | | | | | | OP | Follow-up[2] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Day:* | *–35 to –2* | *–1* | *1* | *2* | *3* | *4* | *5 to 6* | *7* | *8* | *9* | *14 to 16* | *21 to 23* |
| Informed consent | X | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | X | | | | | | | | | |
| Medical history | X | | | | | | | | | | | |
| Admission | | X | | | | | | | | | | |
| Inpatient stay | | ← | — | — | — | — | — | — | → | | | |
| Discharge | | | | | | | | | X | | | |
| Safety assessments | | | | | | | | | | | | |
| Physical examination[3] | X | X | X | | | | | | X | | | X |
| Height & weight[3] | X | X | | | | | | | | | X | X |
| Vital signs[5] | X | X | X | X | | | | X | X | | X | X |
| 12-lead ECG[6] | X | | X | | | | | X | | | | X |
| Serology | X | | | | | | | | | | | |
| Laboratory safety tests[7] | X | X | | X | | | | | X | | X | X |
| Pregnancy[8] | X | X | | | | | | | | | | X |
| FSH test[9] | X | | | | | | | | | | | |
| Urine drug, alcohol and smoking tests | X | X | | | | | | | | | | |
| Spirometry[10] | X | | X | X | | | | X | X | | X | X |
| Nasal examination | X | X | | X | | | | | X | | X | X |
| SARS-CoV-2 infection test[11] | X | X | | | | | | | X | | X | X |
| Self-assessment nasal tolerability rating scale[12] | | | X | X | X | X | X | X | | | | |
| Dosing | | | | | | | | | | | | |
| Intranasal Neumifil[13] | | | X | X | X | X | X | X | | | | |
| Neumifil PK | | | | | | | | | | | | |
| PK sampling[14] | | | X | | | | | X | | | | |
| Immunogenicity | | | | | | | | | | | | |
| ADA sampling[15] | | | X | | | | | | | | | X |
| Pharmacodynamics | | | | | | | | | | | | |
| Nasal wick sampling[16] | | X | | | | | | | X | | | X |
| Ongoing subject review | | | | | | | | | | | | |
| Concomitant medicines | ← | — | — | — | — | — | — | — | — | — | → | |
| AEs | ← | — | — | — | — | — | — | — | — | — | → | |

Abbreviations: OP: outpatient visit; ECG: electrocardiogram; FSH: follicle-stimulating hormone; PK: pharmacokinetics; ADA: anti-drug antibodies; AEs: adverse events.

**Notes:**

1. Screening will be within 35 days before dosing
2. Follow up will be 14 days (± 1 day) after the last dose.
3. Full physical examinations will be done at screening and Day –1. Brief (symptom-directed) physical examinations will be done at all other timepoints. Subjects may be referred for chest x-ray if the chest examination results are of clinical concern.
4. Height measured at screening only.
5. Vital signs consist of: systolic and diastolic blood pressure, heart rate, temperature, pulse oximetry and respiratory rate. They will be assessed at screening; on Day –1, and before and at 2, 4, 8, 12 and 24 h after dosing on Days 1 and 7; at the outpatient visit; and at follow-up. Triplicate measurements (at least 2 min apart) will be made at screening and before dosing. Single measurements will be made at all other time points. Measurements should be made with subjects in a supine position, after resting for 5 min.
6. ECGs will be recorded at screening; before and at 2.5 h after dosing on Days 1 and 7; and at follow-up. Triplicate recordings (to at least 2 min apart) will be made at screening; single recordings will be done at all other time points. Recordings should be made with subjects in a supine position, after resting for 5 min.
7. Laboratory safety tests consist of biochemistry, haematology and urinalysis in serum. They will be done at screening; on Day –1; at 24 h after dosing on Day 1; on Day 8; at the outpatient visit; and at follow-up. Subjects should fast for ≥ 8 h before laboratory safety tests at screening, admission (Day –1), and follow-up.
8. Pregnancy tests in women of child-bearing potential only.
9. FSH tests in post-menopausal women at screening only.
10. $FEV_1$ and FVC will be measured at screening; at 4, 8, 12 and 24 after dosing on Days 1 and 7; at the outpatient visit; and at follow-up.
11. If a subject develops symptoms of COVID-19, ad hoc SARS-CoV-2 infection tests will be done.
12. Self-assessment nasal tolerability questionnaires will be completed at 1 and 12 h post dose after each dose of Neumifil.
13. Once-daily intranasal doses of Neumifil.
14. Blood samples for assay of Neumifil will be taken:
    - before and at 1, 2, and 3 h after dosing on Days 1 and 7
15. Blood samples for assay of Neumifil ADAs will be taken before dosing on Day 1, and at follow-up.
16. Nasal wick samples will be taken before the evening meal on Day –1, or not less than 2 h after food at all timepoints.

When more than one procedure is scheduled at a specific time point, procedures should be done in the following order: ECG, vital signs, blood samples (at the scheduled time), then spirometry. Blood sampling should be done on time. Other procedures should be done as close as possible to the scheduled time point.

## 12.2 Sampling time points and additional tests

With the sponsor's approval, additional time points may be introduced, and changes to time points may be made, if we have reason to believe that the change might improve the quality of the data (for example, if we believe that an important effect of the IMP is occurring at a time when no measurements are scheduled), or if extra procedures are needed in the interest of subject safety. However, the total volume of blood taken in the trial will not exceed the value given in section 12.5. Any additional urine collections may include continuous, total collections, if necessary. An additional 48 hours' residence in the ward, and additional outpatient visits, will be permitted, in the event of a technical failure, and/or if extra observations or samples of blood or urine are needed.

Extra procedures and changes to time points which have a significant impact on the scientific value and/or safety of the trial participants will be implemented only after approval of a substantial amendment from the Regulatory Authority (MHRA), unless the changes constitute an urgent safety measure.

The following will **not** be regarded as protocol deviations.

**Table 5 Acceptable deviation times (Part A)**

| Procedure | Timepoint | Acceptable deviation |
|---|---|---|
| PK blood sampling | Predose on Day 1 | Up to 30 min before dosing |
| | 1 h to 3 h post dose | ± 10 min of the scheduled time |
| All other procedures* | Pre-dose on Day 1 | Up to 90 min before dosing* |
| | Up to and including 4 h post dose | ± 10 min of the scheduled time |
| | After 4 h to 24 h post dose | ± 15 min of the scheduled time |
| | Outpatient visits | ± 1 day |

* samples for urinalysis may be collected anytime from when the subject awakes until the scheduled time.

**Table 6 Acceptable deviation times (Part B)**

| Procedure | Study day | Timepoint | Acceptable deviation |
|---|---|---|---|
| PK blood sampling | Days 1 and 7 | Predose | Up to 30 min before dosing |
| | | 1 h to 3 h post dose | ± 15 min of the scheduled time |
| All other procedures* | Days 1 and 7 | Pre-dose | Up to 90 min before dosing* |
| | | Up to and including 4 h post dose | ± 10 min of the scheduled time |
| | | After 4 h to 24 h post dose | ± 15 min of the scheduled time |
| | Days 2–6 | Predose | Before dosing |
| | Day 8 | > 24 h post dose | ±1 h of the scheduled time |
| | Day 9 onward | Outpatient visits | ± 1 day |

* samples for urinalysis may be collected anytime from when the subject awakes until the scheduled time.

## 12.3 Follow-up

Subjects will return to the ward about 7 (Part A) or 14 (Part B) days after their (final) dose of trial medication for a follow-up visit. Withdrawn subjects who consent to a follow-up visit will undergo the same procedures (see section 9.4).

The follow-up period may be extended if:

1. a subject has an unresolved AE at the follow-up visit, which, in the opinion of the investigator, merits further follow-up; or
2. new information becomes available that supports an extended follow-up period.

The investigator will decide on the nature of the follow-up. For example, subjects may have a telephone follow-up at which they are asked about AEs, or subjects may be asked to attend extra outpatient visits for additional monitoring of effects of IMP, and for extra safety tests. The extra safety tests might include tests that are not described in this protocol. The investigator reserves the right, during or after the study, to repeat safety tests or to do any extra safety tests that are in the best interest of the subjects. Those extra tests may or may not be described in this protocol.

## 12.4 Methods

***Blood collection***

Blood will be taken by venepuncture or via a cannula. Cannulae will be inserted under local anaesthesia with lidocaine 0.5%, for withdrawal of venous blood.

After each blood sample, the cannula will be flushed with 3–5 mL normal saline, to keep it patent. In order to minimise dilution of each subsequent blood sample with normal saline, the following procedure will be used: about 1 mL will be drawn via the cannula into the sampling syringe and discarded. The definitive blood sample will then be taken.

Blood volumes of specific types of samples may vary from those described below, but any change to the sample volumes will not cause the total volume of blood taken during the study to exceed that given in section 12.5.

***Samples for laboratory safety tests***

Blood will be taken for:

- haematology (2 mL in EDTA)
- biochemistry (3.5 mL in tubes with a gelatin plug)
- serology (3.5 mL in tubes with a gelatin plug)
- serum pregnancy/FSH (3.5 mL in tubes with a gelatin plug; serology sample used at screening)

Blood samples will be collected into 13 × 75 mm tubes. Urine will be collected in Universal containers. Samples will then be transferred to the laboratory. For

logistical reasons, blood and/or urine samples may be collected in tubes other than those stated below.

***Processing and analysis of samples for laboratory safety tests***

Processing of samples will be done by the HMR Analytical Laboratory in accordance with the laboratory's SOPs.

The HMR Analytical Laboratory will do safety tests on blood and urine samples using instruments interfaced to a validated laboratory information management system (LIMS). Data from analysers that are not interfaced will be entered manually into the LIMS.

**Table 7 Laboratory safety tests**

**Haematology:**

- haemoglobin (Hb)
- red blood cells (RBC)
- mean corpuscular volume (MCV)
- mean corpuscular haemoglobin (MCH)
- mean corpuscular haemoglobin concentration (MCHC)
- haematocrit
- white blood cells (WBC) and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
- platelets

**Urinalysis:**

- dipstick: protein, blood, ketones, glucose, bilirubin, urobilinogen, leukocyte esterase, specific gravity, nitrites, pH
- microscopy: only if dipstick test for protein, blood, leukocyte esterase or nitrites is abnormal

**Serology:**

- hepatitis B (hepatitis B surface antigen)
- hepatitis C antibody
- hepatitis C RNA[#]
- HIV screen (HIV 1 and 2)

**Biochemistry:**

- urea
- creatinine
- uric acid
- total bilirubin
- total protein
- albumin
- globulin
- alkaline phosphatase (AP)
- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- gamma-glutamyl transpeptidase (GGT)
- glucose*
- phosphate
- cholesterol
- triglycerides
- potassium
- sodium
- calcium
- chloride
- C-reactive protein (CRP)

* fasting at screening, on Day –1 and at Follow-up

[#] performed if result for hepatitis C antibody is positive

***Pregnancy tests***

Serum pregnancy tests will be done using an immunoenzymatic method.

***FSH tests***

Serum FSH tests will be done using a chemiluminescent immunoassay method.

***Drugs of abuse, alcohol and cotinine tests***

Urine will be tested for drugs of abuse, alcohol and cotinine according to the laboratory's SOP. Tests will include: amphetamines, cocaine, opiates, cannabis, barbiturates, benzodiazepines, alcohol and cotinine.

***Processing of blood samples for analysis of plasma concentration of Neumifil***

5 mL blood will be collected in will be taken into $K_2$EDTA tubes, and immediately placed on ice. Samples will be centrifuged at 2000 *G* for 10 min at 4 ºC and divided into 2 aliquots of approximately equal volume (minimum of 200 µL in the primary aliquot) in 1.8 mL screw-capped polypropylene cryotubes. Plasma samples will be frozen at about –70 °C or below within 1 h after collection, and stored until dispatch to Alderley Analytical Ltd for analysis.

***Processing of blood samples for anti-drug antibody analysis***

5 mL blood will be collected in BD Vacutainer® rapid serum 5 mL tubes, and left at room temperature for 5 mins to clot. Samples will be centrifuged at 2000 *G* for 10 min at 4 ºC and stored on ice until they are divided into aliquots. Each sample will be divided into 2 aliquots of approximately equal volume (minimum of 1.5 mL in the primary aliquot) in 2 mL screw-capped polypropylene cryotubes. Serum samples will be frozen at about –70 °C or below within 30 min after collection and stored until dispatch to Kymos for analysis.

***Physical examination***

Physical examination will be done by a physician. Brief physical examinations will be done at the timepoints in the schedule of procedures (section 12.1) if clinically indicated. The following systems/sites will be examined during brief physical examinations: cardiovascular, respiratory, abdomen, nose examination (including rhinoscopy), and other. Full physical examinations will be given at all other timepoints. The following will be examined during full physical examinations: general appearance; head, ears, eyes, nose and throat; thyroid; lymph nodes; back and neck; heart; chest (including auscultation for crepitations and reduced air entry, and percussion for dullness); lungs; abdomen; skin; and extremities; and the following systems will be assessed: musculoskeletal and neurological.

If the chest examination result is of clinical concern, the subject may be referred to a clinic for investigative chest x-ray (Part B only).

***Height and weight***

Height and weight will be measured by trained staff at HMR.

***Vital signs***

***Blood pressure and heart rate*** will be measured using SpaceLabs oscillometric equipment. Measurements will be made with subjects in a supine position; subjects will remain supine for at least 5 min before vital signs are measured.

***Tympanic temperature*** will be measured using digital thermometers.

***Respiratory rate*** will be measured by observation of the chest.

***Peripheral arterial oxygen saturation ($SpO_2$%)*** will be assessed using pulse oximetry.

***Repeat vital signs measurements***

During the trial, if vital signs fall outside the ranges below, a physician will review and decide on an appropriate course of action. The procedure will only be repeated if instructed by a physician.

| | |
|---|---|
| Supine systolic blood pressure: | 90–140 mm Hg |
| Supine diastolic blood pressure: | 40–90 mm Hg |
| Supine heart rate: | 40–100 beats/min |
| Temperature: | 35.5–37.8 °C |
| Respiration rate: | 10–16 breaths/min |

If the result of the repeat measurement is still out of range, the investigator will decide on an appropriate course of action.

***Standard 12-lead ECGs***

12-lead ECGs will be recorded using Mortara ELI250c and ELI280 cardiographs. Each recording will be printed on a single A4 page at paper speed 25 mm/sec and calibrated to 10 mm/mV. Recordings will be made with subjects in a supine position; subjects will remain supine for at least 10 min before the ECG is recorded. PR, RR, QRS and QT intervals will be captured on source documents. QT interval will be corrected using Fridericia's formula (QTcF).

During the trial, if ECG values fall outside the ranges below, a physician will review and decide on an appropriate course of action. The procedure will only be repeated if instructed by a physician.

| | | | |
|---|---|---|---|
| Ventricular rate: | 35–100 beats/min | PR interval: | 110–220 msec |
| QRS: | ≤ 120 msec | QTcF (men): | ≤ 450 msec |
| | | QTcF (women): | ≤ 470 msec |

If the result of the repeat measurement is still out of range, the investigator will decide on an appropriate course of action.

***Forced expiratory volume test***

$FEV_1$ and FVC will be measured using a CareFusion Micro lab MK8 spirometer.

***Nasal examination***

At screening, subjects will be asked whether any part of the nose is tender, sore, or irritating, and whether their sense of smell is normal for them. An external

examination of the nose will be done, and significant abnormalities or erythema will be recorded. A nasal speculum will be used to inspect the nose and assess whether nasal polyps, inflammation or erythema are present.

At specified times during the study, subjects will be asked whether any part of the nose is tender, sore, or irritating, and whether their sense of smell has changed since the start of the study. An external examination of the nose will be done, and abnormalities, inflammation or erythema will be recorded, as well as any changes from baseline (screening), or the previous examination. A nasal speculum will be used to inspect the nose and assess whether abnormalities, inflammation, or erythema are present, as well as any changes from baseline (screening) or the previous examination.

***Subject self-reported dosing experience***

Subjects will complete a self-reported dosing and post-dosing questionnaire. Subjects are asked to assess whether they experienced any of the following using a numerical rating scale from 0 to 10:

- Pain or stinging in the nose
- Burning sensation or sensation of heat/hotness in the nose
- Bleeding from the nose
- Sensation of needing to blow their nose
- General irritation in the nose
- Sneezing
- Marked change in the sense of taste or smell
- Unpleasant taste

To reduce variability, subjects will be able to see their previous responses. A copy of the questionnaire can be found in Appendix 1 (section 22).

***Nasal wick sampling***

Nasal wicks will be used to collect samples of nasal secretions for measurement of cytokines and chemokines (including but not limited to IL-1, IL-3, IL-10, TNF-α, MCP-1 and IP-10), using a multiplex assay.

## 12.5 Total volume of blood removed

The total volume of blood taken from each volunteer in the trial will be about 52 mL in Part A, and 93.5 mL in Part B, as stated in Table 8 (Part A) and Table 9 (Part B), respectively. Additional blood samples for assay of Neumifil plasma concentration, ADAs, or for laboratory safety tests may be taken as described in section 12.2. No more than an extra 80 mL of blood will be taken from any subject.

**Table 8 Planned blood volume (Part A)**

| Test | Planned number of tests | Volume (mL) | Total planned blood volume (mL) |
|---|---|---|---|
| Haematology | 6 | 2 | 12 |
| Biochemistry | 6 | 3.5 | 21 |
| Serology (and FSH) | 1 | 3.5 | 3.5 |
| Pregnancy* | 2 | 3.5 | 3.5 |
| Plasma Neumifil | 4 | 2 | 8 |
| Discard (when using a cannula) | 4 | 1 | 4 |
| | | **Total** | **52 mL** |

**included in serology sample at screening*

**Table 9 Planned blood volume (Part B)**

| Test | Planned number of tests | Volume (mL) | Total planned blood volume (mL) |
|---|---|---|---|
| Haematology | 6 | 2 | 12 |
| Biochemistry | 6 | 3.5 | 21 |
| Serology (and FSH) | 1 | 3.5 | 3.5 |
| Pregnancy* | 2 | 3.5 | 7 |
| Plasma Neumifil | 8 | 5 | 40 |
| ADAs | 2 | 5 | 10 |
| Discard (when using a cannula) | 8 | 1 | 8 |
| | | **Total** | **93.5 mL** |

**included in serology sample at screening*

# 13 Trial materials

## 13.1 Identity of test product

[redacted]

The sponsor will provide to HMR a certificate of analysis for the test product, and, if applicable, any other documents and data required by HMR's Qualified Person (QP) to release batches of IMP.

### 13.2 Packaging and labelling

The trial medication will be prepared, packaged, and labelled by the HMR Pharmacy, in accordance with The Rules Governing Medicinal Products in the European Union, Volume 4: Good Manufacturing Practice (GMP), and with HMR's Manufacturing Authorisation for IMPs (MIA[IMP]). The IMP labels will include all the information required by Annex 13 to GMP[11].

### 13.3 Storage and accountability of IMP

The IMP will be stored and accounted for according to GMP and HMR SOPs.

At the end of the trial, all unused IMP supplies will be returned to the sponsor or destroyed in accordance with the sponsor's instructions. Further details will be provided in the IMP handling manual.

## 14 Adverse events

### 14.1 Definitions of adverse events

*Adverse event (AE)*

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with that treatment.

*Adverse drug reaction (AR)*

All untoward and unintended responses to an IMP related to any dose administered. Note that, according to the ICH Guideline for Good Clinical Practice (ICH GCP), a causal relationship between the medicinal product and the AE is at least a reasonable possibility, ie a relationship cannot be ruled out.

*Unexpected adverse drug reaction*

An AR, the nature or severity of which is not consistent with the applicable product information (eg Investigator's Brochure [IB] for an unauthorised investigational product, or summary of product characteristics for an authorised product).

*Serious adverse event (SAE) or serious adverse drug reaction (SAR)*

An AE or AR that:

- is fatal;
- is life-threatening;

- requires or prolongs inpatient treatment;
- results in persistent or significant disability or incapacity; or
- is a congenital anomaly or birth defect.

*Note:*

the term 'life-threatening' in the definition of 'serious' refers to an event or reaction in which the patient was at risk of death at the time of the event; it does not refer to an event or reaction which hypothetically might have caused death had it been more severe; and

in accordance with the ICH Guideline on Clinical Safety Data Management: Definitions and Standards of Expedited Reporting, events or reactions that are not immediately life-threatening or may not result in death or hospitalisation but might jeopardise the subject or require intervention to prevent one of the other outcomes listed above, should usually be considered serious.

*Significant AE or AR*

An AE or AR which is not serious but is otherwise significant. The following should normally be considered significant:

- a marked haematological or other laboratory abnormality;
- an AE or AR that leads to an intervention, including withdrawal of drug treatment, dose reduction or significant additional concomitant therapy; or
- any AE or AR that the investigator considers to be significant.

## 14.2 Procedures for recording adverse events

Subjects will be carefully monitored for AEs. The investigator or delegate will question the subjects about AEs using a non-leading question, such as 'How are you feeling?'. The investigator will also record AEs reported spontaneously by the subjects. Clinically significant changes in the findings of physical examination, and clinically significant abnormalities in the results of objective tests (eg laboratory variables, ECG) may also be recorded as AEs. Nasal tolerability questionnaire scores > 0 will be recorded as AEs.

The investigator will use the following criteria when deciding whether to report an abnormal result as an AE.

1. The test result is associated with accompanying symptoms.
2. Results of additional diagnostic tests cause concern or necessitate medical intervention.
3. As a consequence of the test result, the subject is withdrawn, or the subject is given concomitant treatment.
4. The investigator considers the result to constitute an AE.

If any of the above criteria are met, the investigator will report the result as an AE.

A record will be kept in the source documents of all AEs as reported, whether believed to be related or unrelated to the treatment. The record will include the following.

- **Clinical symptoms**: a simple, brief description.
- **Date and time of onset and end** of clinical symptoms.
- **Frequency**: constant or intermittent.
- **Severity**. The following categories will be used:

  *Mild:* the AE does not interfere with the volunteer's daily routine and does not require intervention; it causes slight discomfort.

  *Moderate:* the AE interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort.

  *Severe:* the AE results in alteration, discomfort or disability which is clearly damaging to health.

- **Relationship to treatment**: the assessment of relationship of AEs to the administration of IMP is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used.

  *Related*

  An event for which, after careful medical evaluation, a connection with trial medication cannot be ruled out with certainty. The event occurs after exposure to trial medication. The event may occur at a reasonable time in relation to the time of administration of the trial medication but might also be attributable to a commonly occurring alternative cause. Alternatively, the event may not occur at a reasonable time in relation to the time of administration of trial medication but may not be attributable to an alternative cause.

  *Not related*

  An event which occurs before exposure to the trial medication, or which does not occur at a reasonable time in relation to the time of administration of trial medication and can be attributed to a commonly occurring alternative cause. Alternatively, the event is unrelated to the trial (eg road traffic accident), unless it can be demonstrated that the treatment could have caused the event.

- **Action taken**: none, drug treatment, subject withdrawn, other (specified).
- **Outcome**: recovered/resolved, recovering/resolving (or not recovered/not resolved), or unknown.

## 14.3 Procedures for dealing with serious adverse events

In the event of any SAE which, in the investigator's opinion, justifies termination or modification of the trial (see section 8.4), dosing will be stopped and the sponsor's responsible physician will be informed immediately (within 24 h of the investigator becoming aware of the event) by telephone or email, as follows.

Sponsor's responsible physician: [redacted]

Tel: [redacted]

Email: [redacted]

All SAEs occurring after the signing of the ICF until the follow up visit, regardless of study drug relationship, must be reported to the sponsor's pharmacovigilance provider, with as much information as possible, within 24 h of the investigator becoming aware of the event. The investigator will complete a serious adverse event form and provide it to the sponsor's pharmacovigilance (PV) provider immediately (and within 24 hours of becoming aware of the event), via the following contact details.

Diamond PV Services Limited

Email (primary): PVServices@diamondpharmaservices.com

Fax (back-up): +44 (0) 1279 418 964

Tel (back-up): +44 (0) 1279 406 759

The sponsor will also be notified by email [redacted]

The investigator will notify the REC of SAEs that occur during this trial, if applicable, in accordance with the SOPs issued by the Research Ethics Service (RES).

The sponsor is responsible for determining the expectedness of the event, using the reference safety information in the IB. The sponsor will notify the MHRA of all suspected unexpected serious adverse reactions (SUSARs) and will be responsible for ensuring that the REC is notified of SUSARs, if applicable. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the sponsor has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the sponsor has learned of them.

## 14.4 Procedures for handling withdrawals due to adverse events

The investigator will assess the reason for withdrawal as far as possible and will fully record the circumstances and medical details. Provided that subjects give written

informed consent, they will undergo the standard medical examination and laboratory tests at withdrawal from the trial which they would have undergone had they completed it (see also section 9.4).

### 14.5 Procedures for reporting pregnancies

Subjects will be asked to follow the contraception guidance in section 11.

If, during the study, the investigator becomes aware of a pregnancy in a subject or their partner, they will inform the sponsor's pharmacovigilance provider immediately (within 24 h of the investigator becoming aware of the event), as follows.

Diamond PV services Limited

Email (primary): PVServices@diamondpharmaservices.com

Fax (back-up): +44 (0) 1279 418 964

Tel (back-up): Tel (back-up): +44 (0) 1279 406 759

The investigator will follow-up the pregnancy according to HMR SOPs, provided the subject (or their partner) consents to that. A pregnancy will not constitute an SAE unless it meets one of the criteria in section 14.1.

## 15 Data management and quality assurance

CRF source documents will be securely stored within HMR. Data collected in source documents (see section 18.2) will be transcribed into an electronic CRF (eCRF).

The investigator is responsible for ensuring the accuracy and completeness of the data entered into the eCRF, and the timeliness of data entry. Clinical data (including AEs, concomitant medication, etc) will be entered into a 21 CFR Part 11-compliant Medrio M-1 database. The Medrio M-1 system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Data reported in the eCRF, derived from source documents, should be consistent with the source documents or the discrepancies should be explained. Where the data violate data validation checks, queries will be generated for resolution by clinical staff. All edits made to the database upon resolution of queries will be recorded in an electronic audit trail.

The database will be locked after the following have been completed: all expected eCRF data have been entered and accounted for; all discrepancies have been resolved; data have been coded as appropriate; SAEs have been reconciled; all site audit findings impacting the database have been closed; and quality control (QC) inspection has been completed.

Data in source documents will be checked by the HMR Quality Assurance (QA) Department. In addition, the HMR QA Department will audit the trial report; that

audit will include checks to ensure that statistical output is correctly reproduced in the report. If requested, the investigator will provide the sponsor, MHRA, and REC with direct access to the original source documents.

# 16 Statistical methods

## 16.1 Statistical methods

### *16.1.1 Planned analyses*

Final statistical analysis will be done by HMR. A statistical analysis plan (SAP) will be prepared by the HMR Statistics and Data Management Department after completion of the final protocol and before first database lock.

All statistical analysis and reporting will be done using SAS 9.4.

### *16.1.2 Statistical hypotheses*

The trial is an exploratory one, and there are no null hypotheses to be tested.

### *16.1.3 Analysis populations*

The following populations will be identified:

| | |
|---|---|
| *Safety population*: | All subjects who received at least 1 dose of study drug. |
| *PK concentration population*: | All subjects who received at least 1 dose of study drug and for whom a PK sample has been analysed. |
| *PK parameter population*: | All subjects in the PK concentration population for whom PK parameters can be derived. |
| *PD population:* | All subjects in the safety population for whom a PD measure is available. |
| *Immunogenicity population*: | All subjects who received at least 1 dose of study drug and for whom an ADA sample has been analysed (Part B only). |

The primary endpoints will be analysed using the safety population for each study part.

In all populations, treatment will be assigned based upon the treatment subjects actually received, regardless of the treatment to which they were randomised.

### *16.1.4 General considerations for data analyses*

The minimum set of summary statistics for numeric variables will be: n, mean, standard deviation (or standard error), median, minimum, and maximum. 95% confidence intervals will be presented where appropriate for data interpretation.

Categorical data will be summarised in frequency tables with n and percentage. Summaries of a categorical variable will include all recorded values.

The minimum and maximum values will be presented to the same number of decimal places as the raw data collected in the CRF (or to 3 significant figures for derived parameters). The mean, median and percentiles (eg Q1, and Q3) will be presented to one additional decimal place. The standard deviation and standard error will be presented to 2 additional decimal places.

'Baseline' will be the latest value obtained before IMP administration (predose on Day 1, or Day –1 if not recorded at predose, or screening if not recorded at predose or on Day –1 [eg weight]). Out-of-range laboratory tests may be repeated. If a test is out of-range at baseline and repeated before dosing, the latest repeat value before dosing will be used as baseline. However, if a test is out-of-range and repeated at any other time during the study, the out-of-range value (not the repeat value) will be included in statistical summaries.

### *16.1.5 Study population analyses*

#### *16.1.5.1 Disposition of subjects*

The disposition of all subjects in the safety population will be summarised including: number of subjects randomised; number completing the study, by treatment; and number discontinued from the study.

All subjects who withdraw or are withdrawn from the study will be listed, by treatment, with the reason for withdrawal.

#### *16.1.5.2 Demographic and baseline characteristics*

Demographic and baseline characteristics (eg physical examination, vital signs and ECGs) will be summarised.

Subjects who take concomitant medication will be listed.

#### *16.1.5.3 Treatment compliance*

Dates and times of dosing will be listed.

### *16.1.6 Safety data analyses*

Summaries and listings of safety data will use the safety population.

#### *16.1.6.1 Adverse events*

AEs will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) current at the time of database lock.

All AEs will be listed.

A treatment-emergent adverse event is an AE that emerges during treatment (having been absent before treatment) or that worsens after treatment[12].

The number of subjects with at least one TEAE will be tabulated by actual treatment and MedDRA system organ class and preferred term.

For each of the following, the number of TEAEs and the number of subjects with TEAEs will be summarised by actual treatment as follows:

- TEAEs, by system organ class and preferred term
- TEAEs by system organ class, preferred term and severity
- drug-related TEAEs, by system organ class and preferred term

Subjects with more than one TEAE will be counted only once, at the maximum causality, for each system organ class and preferred term. AEs with missing severity and/or causality will be treated as severe and possibly related, respectively.

AEs leading to withdrawal, deaths and other SAEs will be listed separately (fatal events will be listed separately from non-fatal events).

#### *16.1.6.2 Clinical laboratory evaluations*

Data from haematology and clinical chemistry will be summarised by treatment.

Any laboratory value outside the reference interval for that variable will be flagged with an ‘H’ if it is higher than the reference interval, and with an ‘L’ if it is lower. Additionally, if, during the course of the trial, a variable changes from baseline by more than a predetermined amount (as defined by the principal investigator), that value will receive a flag ‘I’ if increased, or ‘D’ if decreased. Therefore, if a value both falls outside the reference interval and alters from the baseline value by more than the predetermined amount, it will attract a double flag and will be considered to be of potential clinical importance (PCI).

All laboratory values of PCI will be listed. In a separate listing, laboratory values of PCI will be listed with all related laboratory results (ie haematology or clinical chemistry). Frequencies of laboratory values of PCI will be summarised.

#### *16.1.6.3 Other safety measures*

Vital signs at each planned assessment and change in vital signs from baseline at each planned post baseline assessment, will be summarised by actual treatment.

Vital signs of PCI will be listed separately.

QT interval will be corrected using Fridericia's (QTcF) formulae.

ECG variables will be summarised by treatment and time point. Differences from baseline will be summarised by treatment and time point.

QTcF > 450 msec and increases in QTcF from baseline (Day 1 predose) of > 30 msec will be considered to be of PCI. The number of subjects with a QTcF value of PCI will be summarised by actual treatment and time point, giving the numbers of subjects with QTcF > 450 msec, > 480 msec and > 500 msec, and the numbers of subjects with increases in QTcF from baseline of > 30 msec and > 60 msec[13]. A supporting listing of all subjects with a QTcF value of PCI, and a separate listing of ECG findings classified as abnormal by the investigator, will also be provided.

Abnormal physical examination findings, (including nasal examination findings) will be listed.

#### *16.1.6.4 Immunogenicity assessment (Part B only)*

Analyses of ADAs to Neumifil will be listed and summarised by treatment group and timepoint. This analysis will be reported separately to the clinical study report.

### *16.1.7 Plasma concentration data analyses*

Neumifil plasma concentration data will be listed by treatment and time point.

### *16.1.8 Pharmacodynamic data analyses (Part B only)*

Presence of cytokines and chemokines will be listed and summarised by treatment and timepoint.

PD concentrations at each planned assessment and change in PD concentrations from baseline at each planned post baseline assessment, will be summarised by actual treatment.

## 16.2 Determination of sample size

Since this is a pilot trial, no formal sample size determination is appropriate.

# 17 Ethical and regulatory requirements

The trial proposal will be reviewed by a recognised REC, and by the MHRA. The trial will not proceed unless the sponsor obtains from the MHRA a clinical trial authorisation (CTA), and the REC gives a favourable opinion of the trial.

The trial will be done at HMR, in compliance with The Medicines for Human Use (Clinical Trials) Regulations 2004 and current amendments[15], The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019[16], The

Human Medicines (Amendment etc) (EU Exit) Regulations of 2019 and 2020[17,18], GMP[11], the SOPs issued by RES for RECs in the UK[19], and Good Clinical Practice, which has its origins in the Declaration of Helsinki.

All subjects must give written consent to participate in this trial. Consent for screening evaluations may be obtained using the information and consent form for the HMR healthy volunteer panel, which has been approved by the Health Research Authority's Generic Document Review Committee. The trial specific information and consent form will be signed by the subject either before any screening evaluation or after the investigator confirms the eligibility of the subject for the trial and before the subject is randomised to receive the first administration of IMP. Before giving consent, subjects must read the information sheet about the trial. They must also read the consent form. They will then discuss the trial with the investigator or his deputy and be given the opportunity to ask questions. The trial-specific information sheet and the consent form must be approved by the REC.

Each subject is free to withdraw from the trial at any time, without giving a reason. If a subject withdraws, the investigator will ask the subject to consent to a follow-up examination. For withdrawn subjects, the investigator will use a special information and consent form which has been ethically approved. If the subject consents to the follow-up examination but asks the investigator to destroy all identifiable samples taken from the subject and/or not enter into the eCRF results of the follow-up examination, the investigator will comply with the subject's requests.

The sponsor will ensure that the MHRA and the REC, are informed promptly of SUSARs (see section 14.3), and that any new reports of SUSARs from other ongoing trials of the IMPs under investigation in this trial are notified to the MHRA, and to the REC, if applicable. The sponsor will provide the investigator, the REC and the MHRA with annual safety reports of the IMP under investigation, and listings of all suspected serious adverse reaction (SSAR) reports. The sponsor will also inform the investigator promptly of any new safety or toxicology data that might affect the safety of the subjects in this study.

The investigator will promptly inform the sponsor and, if applicable, the REC of any SAE that occurs during this trial (see section 14.3). The investigator will provide the REC with annual progress reports of the trial, if the trial lasts longer than a year.

The investigator will report to the REC any protocol deviation that is, in his opinion, of clinical significance. The investigator will also inform the REC in the event of several deviations which, although of no clinical significance, cause inconvenience and/or discomfort to the volunteers. The sponsor will notify the MHRA and REC of any serious breach of good clinical practice (for example, the investigator puts subjects' safety at risk, falsifies data, or persistently fails to comply with this protocol or good clinical practice).

Within 90 days after the end of the trial, the sponsor (or sponsor's delegate) will ensure that the REC and the MHRA are notified that the trial has finished. If the trial

is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The sponsor will supply a summary of the clinical trial report to the MHRA and REC within 1 year after the end of the trial.

Trial procedures at HMR will be subject to audits by the HMR QA Department, to ensure compliance with the protocol and applicable regulatory requirements.

# 18 Trial documentation

## 18.1 Protocol amendments

After the protocol has been approved by the REC and the MHRA, no changes may be made without the agreement of both the investigator and the sponsor.

The MHRA and REC do not need to approve any substantial change to the protocol that needs to be implemented urgently to avoid an immediate hazard to trial subjects. The sponsor will ensure that the MHRA and REC are informed of urgent amendments in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 and current amendments[15] and the SOPs issued by RES for NHS RECs[15].

All agreed protocol amendments will be recorded on a written agreement which will be signed and dated by the investigator and sponsor, and attached to the original protocol. The REC and/or MHRA must approve substantial amendments before they are implemented.

The standard text in our information and consent form template explains that the planned doses may change during the trial, and that we may give the subjects any dose that has been approved by the MHRA and REC for the trial. However, if we want to reduce the planned dose, we consider it essential to fully inform the subject of our reasons, because a reduction in dose might be due to poor tolerability, and that might affect the subject's decision to remain in the trial. Wherever possible, we will obtain prior approval from the REC for the information and consent form that we give to subjects before we reduce the dose. But, owing to the nature of trials on healthy volunteers, it is likely that we will sometimes have to implement an urgent amendment to lower the planned dose, to avoid immediate hazard to the subjects. We will fully inform the subjects of the reason for reducing the dose and will notify the REC and MHRA promptly of the urgent amendment, in accordance with statutory requirements.

## 18.2 Case report forms

The eCRF will be designed and produced by HMR.

To preserve confidentiality, the CRF will not bear the subject's name. The subject number and/or HMR volunteer number will be used for identification. Age (year of birth) will be collected on the eCRF, not full date of birth.

Data entry into the eCRF is described in section 15.

*Source documents*

Before the start of the study, the sponsor and investigator will sign an agreement listing the source documents to be used in this trial.

### 18.3 Reporting of results

HMR will prepare a draft report for discussion with the sponsor. The report will contain results and discussion of the trial, to which will be attached tables, figures and listings in compliance with ICH E3[20].

Completed eCRFs will be supplied separately to the sponsor by HMR.

## 19 Obligations of the sponsor and investigator

### 19.1 Monitoring, auditing and inspection

The trial will be monitored by the sponsor.

A sample of documents generated by HMR which form part of this trial, and the ensuing data, will be audited by the HMR Quality Assurance Department to assess compliance with the quality management system of HMR. That system incorporates the requirements of The Medicines for Human Use (Clinical Trials) Regulations 2004 (and current amendments)[15], ICH GCP, GMP[11], and the SOPs issued by RES for RECs in the UK[19], and is based on ISO 9001.

The sponsor may do a quality assurance audit, and regulatory authorities may inspect this study, at any time during or after the study. The sponsor and investigator agree to allow auditors and inspectors direct access to all relevant documents, and to allocate time to discuss findings with the auditors or inspectors.

### 19.2 Compensation of volunteers

The sponsor agrees to abide by the Association of the British Pharmaceutical Industry (ABPI) Guidelines for medical experiments in non-patient human volunteers (2018 edition)[21], and undertakes to compensate the subjects for injuries which are considered, on the balance of probabilities, to have arisen as a result of their participation in the trial.

### 19.3 Confidentiality

All personal details of the participating subjects and the results of the trial will be kept strictly confidential. Each subject's GP (or equivalent physician) will be informed of the nature and timing of the trial.

All unpublished documents including the protocol, the CRF, and the IB are confidential. Those documents cannot be disclosed to a third party without the written consent of the sponsor. However, submission of those documents to a REC is expressly permitted.

The investigator agrees that the sponsor maintains the right to use the results of this trial, in their original form and/or in a global report, for submission to governmental and regulatory authorities of any country.

### 19.4 Publication

If the data merit, the investigator and the sponsor will discuss the preparation of a manuscript for publication in a peer-reviewed professional journal or an abstract for presentation, oral or written, to a learned society or symposium. Either party may undertake the task, but both must agree to the strategy before the work is started. Each party will allow the other 30 days to comment before any results are submitted for publication or presentation. Authorship should reflect work done by the investigators and personnel of the sponsor, in accordance with generally recognised principles of scientific collaboration.

### 19.5 Archiving

The sponsor and HMR will keep in a trial master file all the essential documents required by GCP. HMR will ensure that the investigator's master file, and all data generated during the trial, will be archived in a secure place for 15 years. Documents will be stored such that they are readily available for inspection at the request of the sponsor or a regulatory authority. Any transfer of ownership of the investigator's data or documents will be documented, and the sponsor will be informed.

## 20 Premature termination of the trial

The sponsor and investigator reserve the right to terminate this trial should severe AEs, SAEs or any other safety issue occur during the trial. If the trial is terminated prematurely, and the sponsor or investigator, as appropriate, will provide a written statement of the reasons for termination. The sponsor will ensure that the MHRA and REC are notified, as described in section 18.

# 21 References


1. Jang, HJ and Seong, BL (2019). The Quest for a Truly Universal Influenza Vaccine. *Front Cell Infect Microbiol*. 10; 9: 344
2. Haq, K and McElhaney, JE (2014). Immunosenescence: Influenza vaccination and the elderly. *Curr Opin Immunol*. Aug; 29: 38–42.
3. Hoffmann, M. Kleine-Weber, H; Schroeder, S; Krüger, N; Herrler, T; Erichsen, S; Schiergens, T.S; Herrler, G; Wu, N. H; Nitsche, A; Müller, M. A; Drosten, C; Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 181: 271–280
4. Zhou, P. Yang, X. L; Wang, X. G; Hu, B; Zhang, L; Zhang, W; Si, H R; Zhu, Y; Li, B, Huang, C L; Chen, H D; Chen, J; Luo, Y; Guo, H; Jiang, R D; Liu, M Q; Chen, Y; Shen, X R; Wang, X; Zheng, X S; Zhao, K; Chen, Q J; Deng, F; Liu, L L; Yan, B; Zhan, F X; Wang, Y Y; Xiao, G F and Shi, Z L. (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 579; 270–273
5. Shajahan, A. Supekar, N. T. Gleinich, A. S. and Azadi, P. (2020). Deducing the *N*- and *O*- glycosylation profile of the spike protein of novel coronavirus SARS-CoV-2. *Anal. Glycobiol.* 30, 12: 981–988
6. Casalino, L. Gaieb, Z; Goldsmith, J. A. Hjorth, C. K; Dommer, A. C; Harbison, A. M; Fogarty, C A; Barros, E. P; Taylor, B. C; McLellan, J. S; Fadda, E and Amaro, R. E. (2020). Beyond Shielding: The Roles of Glycans in the SARS-CoV-2 Spike Protein *ACS Cent. Sci*. 6: 1722–1734
7. Connaris H, Govorkovab, E. A; Ligertwood, Y; Dutiac, B. M; Yanga, L; Taubera, S; Taylora, M. A; Aliasa, N; Hagana, R; Nashc, A. A; Websterb, R. G and Taylor, G. L. (2014). Prevention of influenza by targeting host receptors using engineered proteins. *PNAS* 111: 6401–6406
8. Emami, A. Tepper, J. Short, B. Yaksh, T.L. Bendele, A.M. Ramani, T. Cisternas, A.F. Chang, J.H. and Mellon, R.D. (2018). Toxicology evaluation of drugs administered via uncommon routes: intranasal, intraocular, intrathecal/intraspinal, and intra-articular. *Int J Toxicol* 37(1): 4–27
9. Mowat, V. Alexander, D.J. and Pilling A.M. (2017). A comparison of rodent and nonrodent laryngeal and tracheal bifurcation sensitivities in inhalation toxicity studies and their relevance for human exposure. *Toxicol Pathol* 45: 216–22
10. Clinical Trials Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials, dated 21 September 2020.

11. The Rules Governing Medicinal Products in the European Union, Volume 4 – Good Manufacturing Practice, incorporating Directive 2003/94/EC.
12. Statistical principles for clinical trials. ICH harmonised tripartite guideline E9, 1998.
13. Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. ICH Guidance for Industry E14, 2005.
14. Julious, SA & Debarnot, CAM (2000) "Why are Pharmacokinetic Data Summarised by Arithmetic Means?", Journal of Biopharmaceutical Statistics, 10(1): 55-71.
15. The Medicines for Human Use (Clinical Trials) Regulations 2004: Statutory instrument 2004 No. 1031, as amended by: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (Statutory instrument 2006 No. 1928), The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006 (Statutory Instrument 2006 No. 2984), The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 (Statutory Instrument 2008 No. 941), The Medicines for Human Use (Miscellaneous Amendments) Regulations 2009 (Statutory instrument 2009 No. 1164), and The Medicines for Human Use (Advanced Therapy Medicinal Products and Miscellaneous Amendments) Regulations 2010 (Statutory instrument 2010 No. 1882), and The Human Medicines Regulations 2012 (Statutory instrument 2012 No. 1916).
16. The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations (2019): Statutory instrument 2019 No 744.
17. The Human Medicines (Amendment etc) (EU Exit) Regulations 2019: Statutory instrument 2019 No 775.
18. The Human Medicines (Amendment etc) (EU Exit) Regulations 2020: Statutory instrument 2019 No 1488.
19. Standard operating procedures for Research Ethics Committees in the UK, Research Ethics Service.
20. Structure and content of clinical study reports. ICH harmonised tripartite guideline E3, 1995.
21. Guidelines for Phase 1 Clinical Trials, 2018 Edition. Association of the British Pharmaceutical Industry.

# 22 Appendix 1: Subject self-reported dosing and post-dosing experience

**Study PNG-NMF-101**

**Subject Number:**

Please assess the following aspects of your dosing and post dosing experience, following administration of Neumifil or placebo. A numerical score of 0 to 10 is used for each parameter, as described below

The statements are as follows.
Since your last dose have you experienced any of the following? –

**1. Pain or stinging in the nose?**

**Score**
0 No Pain or stinging in the nose has been experienced

10 Pain or stinging most extreme imaginable and you would not want to experience it again

**2. Burning sensation or sensation of heat/hotness in the nose?**

**Score**
0 No Burning sensation or sensation of heat/hotness in the nose has been experience

10 Burning sensation or sensation of heat/hotness in the nose most extreme imaginable and you would not want to experience it again

**3. Bleeding from the nose.**

**Score**
0 Bleeding has not experienced

10 Bleeding that requires medical intervention and packing of the nose.

**4. Sensation of needing to blow your nose?**

**Score**
0 The sensation of needing to blow your nose has not been experienced

10 The sensation to blow your nose is persistent and affects your normal life to the extent you would not want to experience it again

**5. General irritation in nose.**

**Score**
0 No irritation has been experienced

10 Irritation of the nose is the most extreme imaginable and you would not want to experience it again

**6. Sneezing**

☐ **Score**
0 Sneezing is not experienced

10 Sneezing most extreme imaginable and you would not want to experience it again

**7. Marked change in your sense of smell or taste**

☐ **Score**
0 No change in your sense of smell or taste

10 Complete loss of smell or taste

**8. Unpleasant taste.**

☐ **Score**
0 No unpleasant taste

10 Unpleasant taste is so bad you would not want to experience it again