CLINICAL STUDY PROTOCOL

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TITLE PAGE
CLINICAL STUDY PROTOCOL

Protocol Number	**COV01**	
EudraCT Number	N/A	
Universal Trial Number	N/A	
IND Number	Not yet assigned	
Study Title	A Phase 1, Single-site, Open-label Study to Determine the Safety and Tolerability of Single and Multiple Doses of Intranasally Administered LMN-301 in Healthy Volunteers	
Overall Study Phase	Phase I	
Investigational Product	LMN-301	
Route of Administration	Intranasal (IN)	
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Version	v1.0, 25 May 2023	

CONFIDENTIALITY STATEMENT
Information contained in this study protocol is confidential and should not be disclosed, without written authorisation from Lumen Bioscience, Inc.

SPONSOR SIGNATURE PAGE

Study Title: A Phase 1, Single-Site, Open-Label Study to Determine the Safety and Tolerability of Single and Multiple Doses of Intranasally Administered LMN-301 in Healthy Volunteers

Signature of Sponsor Representative	***Date***
Carl Mason, MD	
Printed Name of Sponsor Representative	
Vice President, Clinical	
Sponsor Representative Role/Designation	
By my signature, I confirm that I have reviewed this protocol and find its content to be acceptable.	

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Study Title: A Phase 1, Single-Site, Open-Label Study to Determine the Safety and Tolerability of Single and Multiple Doses of Intranasally Administered LMN-301 in Healthy Volunteers

DocuSigned by: *Xiu Qin Lim* Signer Name: Xiu Qin Lim Signing Reason: I approve this document Signing Time: 25-May-2023 | 14:47 ACST 0305F6142B3042BC9C4A2FCCD22A534D	25-May-2023 | 14:48 ACST
Signature of Site Principal Investigator	***Date***
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By my signature, I confirm that I have read the protocol, I understand it, and I agree to personally conduct and supervise the conduct of this study in compliance with the protocol, Human Research Ethics Committee (HREC) procedures, instructions from Lumen Bioscience, Inc, the Declaration of Helsinki, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice Guidelines, and local regulations governing the conduct of clinical studies.	

1 PROTOCOL SYNOPSIS

Study Title	A Phase 1, Single-Site, Open-Label Study to Determine the Safety and Tolerability of Single and Multiple Doses of Intranasally Administered LMN-301 in Healthy Volunteers.
Protocol Number	**COV01**
Phase	I
Number of Clinical Sites	1
Investigational Product	LMN-301
Mode of Administration	Intranasal (IN)
Dose Range	• Part A: single fixed dose of 50 mg IN (25 mg in each nostril) using the Unidose (UDS) Powder Nasal Spray System device (Aptar) on Day 1 • Part B: multiple fixed doses of 50 mg (25 mg in each nostril) using the Unidose (UDS) Powder Nasal Spray System device (Aptar)
Number of Doses	• Part A: Single dose on Day 1 • Part B: o Group 1: once every third day for 12 days (4 doses total), o Group 2: once every other day for 12 days (6 doses total) o Group 3: once every day for 12 days (12 doses total)
Study Population	Healthy adult volunteers aged 18-65 years, with BMI between 18.0 and 30.0 kg/m^2, and maximum body weight of 120 kg. Additional selection criteria apply as described in the study inclusion and exclusion criteria (refer Protocol Section 7).
Study Rationale	SARS-CoV-2 infection is initiated by binding of the receptor binding domain (RBD) on the virus spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor on the target cell membrane. The nasal cavity contains a high SARS-CoV-2 viral load and the intranasal epithelium is considered an important entry portal for the virus. Anti-viral drugs may complement the role of vaccines in the prevention of SARS-CoV-2 infection, by directly delivering biologic neutralization agents that are immediately effective upon administration and can act independently of the host's immune system. Spirulina (Arthrospira platensis) is a type of blue-green algae capable of high expression levels of therapeutic proteins. Spirulina extract powders containing pathogen neutralizing proteins may serve as an effective antiviral drug. Lumen Bioscience has developed methods to genetically engineer spirulina for large-scale biologics manufacturing, and has developed processes to generate a shelf-stable dried spirulina extract containing bioactive protein. Lumen

	proposes to intranasally deliver anti-SARS-CoV-2 viral-binding proteins to the upper airway mucosa using a dry powder inhaler. The product objective is to prevent disease in uninfected individuals and potentially block transmission from infected individuals to others.

Study Objectives and Endpoints		
	Objectives	**Endpoints**
Primary	To determine the safety and tolerability of single and multiple doses of intranasally delivered LMN-301	• Safety and tolerability of single and multiple doses of intranasally administered LMN-301 as measured by: o The occurrence of solicited AEs for 28 days after the first dose of LMN-301 o The occurrence of unsolicited AE/SAEs for up to 28 days after the first dose of LMN-301 o Discontinuation o Changes from baseline in vital signs, safety laboratory parameters, ECG parameters and nasal symptoms using the Sino-nasal outcome test
Secondary	To determine the persistence profile of LMN-301 in the nasal mucosa following single and multiple doses	• Detect the presence of LMN-301 in nasal mucosal lining fluid samples collected from study participants
Exploratory	To detect the presence of LMN-301 and anti-drug antibodies in serum	• Detection of LMN-301 virus-binding proteins and, if virus-binding proteins are detected, anti-virus binding protein IgG in serum samples

Overall Study Design	This is a Phase I, open-label, single site study of LMN-301 administered intranasally as single or multiple doses in healthy volunteers. This study will be conducted in two parts. *Part A (Sentinel, Single-Dose Cohort)* On Day 1, 5 participants will be administered a single dose of LMN-301 IN to each nostril at a fixed dose of 50 mg (25 mg in each nostril) using the Unidose (UDS) Powder Nasal Spray System device (Aptar). Participants will be observed as in-patients for at least 24 hours, and then followed on an outpatient basis for 14 days. Protocol-specified evaluations and procedures will be performed on Days 1-2 and then weekly or bi-weekly. The safety and tolerability data collected from the sentinel cohort participants will be reviewed by the principal investigator (PI), the independent medical monitor, and the sponsor medical monitor, either via email or meeting if required. The PI will decide whether to move forward with the multiple-dose

	cohorts (Part B). *Part B (Multi-Dose cohort)* Up to 30 participants will be sequentially assigned to one of three dosing groups (10 participants per group) starting with Group 1. Participants will be administered LMN-301 IN to each nostril at a fixed dose of 50 mg (25 mg in each nostril) every third day for 12 days (Group 1), every other day for 12 days (Group 2) or every day for 12 days (Group 3). All study participants will be observed in the clinic for 4 hours after the first dose. Throughout the treatment period, participants will be monitored for the occurrence of any adverse events (AEs) and serious adverse events (SAEs). Vital signs, physical exams and safety/laboratory testing will be performed on Days 1, 3 or 4, 7, 10 or 11, and 14. Participants will use a diary (paper or electronic) to record concomitant medication usage and any symptoms from the first dose through 28 days after the first dose. Macroscopic nasal examination will be performed by conventional anterior rhinoscopy and nasal symptoms and social/emotional consequences will be assessed using the Sino-nasal outcome test (SNOT-22). Serum will be collected on Days 1 (baseline before dosing and 2 hours after dosing), 3 or 4, 7 and 14 for analysis to detect systemic absorption of virus-binding proteins and anti-drug antibodies (ADA). Nasal mucosal lining fluid (MLF) samples will be collected using Synthetic Absorptive Matrix (SAM) strips (Nasosorption™ FX·I, Hunt Developments (UK) Ltd, United Kingdom) from all participants on Day 1 (baseline before dosing and 2 hours after dosing), and on Days 3 or 4, 7 and 14. Nasal MLF samples will be sent to Lumen Bioscience (Seattle, WA, USA) for analysis.
Safety Review	There is no safety review committee for this study, however safety and tolerability data collected from the sentinel cohort participants will be reviewed by the principal investigator, the medical monitor, and the sponsor medical monitor, to decide whether to move forward with the multiple-dose cohorts (Part B). The discussion will include review of the study and individual stopping rules. The PI will make the final decision regarding moving forward with the multiple dose cohorts, taking into account recommendations from the medical monitor and the sponsor medical monitor. If stopping criteria are met in Part B, dosing will stop and the principal investigator, the medical monitor, and the sponsor medical monitor will review safety and tolerability data and decide whether to proceed with dosing.
Number of Participants	A total of 35 participants are planned to be enrolled as follows: • Part A: Up to 5 participants • Part B: Up to 30 participants across 3 groups (10 participants per group)
Study Duration	The expected duration of participant engagement is as follows: • Part A: Up to 42 days, inclusive of 28 day screening window. • Part B: Up to 56 days, inclusive of 28 day screening window.
Study Procedures	<u>Baseline, Safety and Tolerability Assessments</u> • Demographics (age, race, sex, and ethnicity) • Medical history

	• Prior and concomitant medication assessments • Physical examination • Nasal examination • Height, weight, and calculation of Body Mass Index (BMI) • Vital signs (systolic and diastolic blood pressure, pulse rate, oral temperature, respiration rate) • ECG • Urinalysis • COVID-19 rapid antigen testing (prior to IP administration) • Serum (Screening) and urine (prior to first study drug administration) pregnancy test (women of child-bearing potential only) • FSH levels (post-menopausal women only) • Viral serology (HIV antibody, HBsAg and HCV antibody) • Urine toxicology screen for drugs of abuse • Solicited adverse events (stuffy nose, runny nose, sneezing, nasal irritation, nasal tenderness/pain, loss of smell, sore/scratchy throat, cough) • Unsolicited adverse events • Sino-nasal outcome test (SNOT-22) • Clinical laboratory safety assessments (hematology, serum chemistry and coagulation) <u>Pharmacokinetic Assessments</u> • Whole blood (serum) • Nasal mucosal lining fluid (MLF) <u>Immunogenicity Assessments</u> • Whole blood (serum) anti-drug antibodies
Statistical Analyses	Detailed methodology for summaries and statistical analyses of the data collected will be documented in a separate Statistical Analysis Plan (SAP). In general, summaries will be presented separately for Parts A and B, with summaries presented by treatment group and overall for Part B. For descriptive statistics, continuous data will be summarised by treatment arm and time point using the number of observations, arithmetic mean, standard deviation (SD), median, minimum and maximum. Discrete data will be summarised using counts and percentages. All available data will be included in data listings. Data tabulations will be performed for specific analysis populations. Demographic data (including gender, age, race, ethnicity, height, weight, and BMI) will be summarised using descriptive statistics. Medical history will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) All AEs will be coded using the latest version of MedDRA by system organ class and preferred term, classified from verbatim terms. Observed values and changes from baseline for vital signs, clinical laboratory parameters and ECG parameters will be summarised at each scheduled timepoint using descriptive statistics. Physical examinations and nasal examination findings will be listed;

	any clinically significant post-dose findings will be recorded as AEs. Individual participant LMN-301 concentrations in plasma and nasal mucosal lining fluid will be listed and summarised using descriptive statistics (n, mean, standard deviation, coefficient of variation [%CV], minimum, maximum, median, geometric mean and geometric coefficient of variation). Due to the sparseness of the PK sampling scheme, no PK parameters will be determined. Serum anti-LMN-301 antibody (possibly binary yes/no, titer, neutralizing) on Day 0 (predose), Day 1 (post dose), Day 3 or 4 (predose), Day 7 (predose) and Day 14 will be reported for each subject and presented tabular and/or graphical form. Changes from baseline in individual total SNOT-22 scores will be calculated as the post-baseline value minus the baseline value and summarised using descriptive statistics.

2 TABLE OF CONTENTS

2.1 List of Tables

2.2 List of Figures

3 LIST OF ABBREVIATIONS AND TERMS

ACE2	Angiotensin-Converting Enzyme 2
ADA	Anti-Drug Antibodies
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification
CFR	Code of Federal Regulations
Covid-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
cGMP	Current Good Manufacturing Practices
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GRAS	Generally Regarded as Safe
HREC	Human research ethics committee
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
INR	International Normalised Ratio
IP	Investigational Product
IUD	Intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
MLF	Mucosal Lining Fluid
NCS	Not Clinically Significant
OTC	Over the Counter
PI	Principal Investigator
PK	Pharmacokinetic
PLOS	Public Library of Science
PT	Preferred Term
PT/PTT	Prothrombin Time/ Partial Thromboplastin Time
QTcF	QT interval corrected by Fridericia formula

RBD	Receptor Binding Domain
RR	Respiratory Rate
SAE	Serious Adverse Event
SAM	Synthetic Absorptive Matrix
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	SARS-associated coronavirus 2, the virus the causes Covid-19
SD	Standard Deviation
SoA	Schedule of Assessments
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
UDS	Aptar Unidose Powder Nasal Spray System Device
US FDA	United States Food and Drug Administration
VHH	Binding Domain Fragment of a Single-Domain Camelid Antibody

4 INTRODUCTION

4.1 Background Information and Rationale

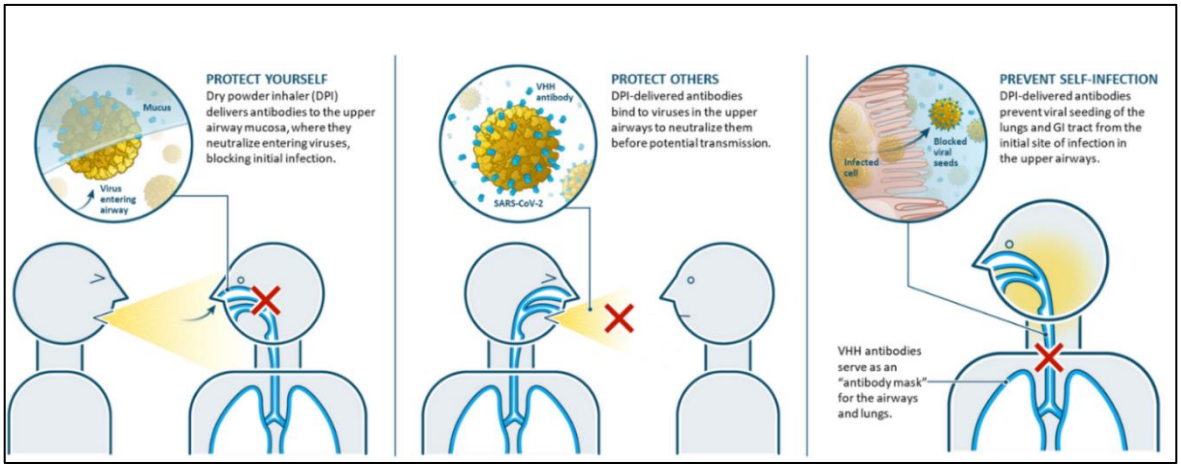
SARS-CoV-2 infection is initiated by binding of the receptor binding domain (RBD) on the virus spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor on the target cell membrane (Jackson et al. 2022). The nasal cavity contains a high SARS-CoV-2 viral load and the intranasal epithelium is considered an important entry portal for the virus (Higgins et al. 2020; Sungnak et al. 2020).

Antiviral drugs complement the role played by vaccines in public health. Rather than eliciting a neutralizing response from the host immune system, antiviral drugs directly deliver biologic neutralization agents that are immediately effective upon administration and can act independently of the host's immune system. Despite the advantages of antiviral drugs, the high cost and limited scalability of biologics manufacturing has prevented widespread adoption.

Spirulina (Arthrospira platensis) is a type of blue-green algae. It is capable of high expression levels of therapeutic proteins and requires only water, light, CO_2 and mineral salts for its production environment. Because the manufacturing pipeline is comprised solely of growing and drying spirulina biomass, it reduces or eliminates the technical challenges and expenses associated with downstream drug processing. This results in a cost-effective system that finally makes it feasible to deliver daily doses of protein therapeutics at mass scale.

Lumen Bioscience developed the methods to genetically engineer spirulina for large-scale biologics manufacturing. Initial therapeutic spirulina products were formulated for oral administration, and in vivo efficacy has been demonstrated in multiple studies (Jester, et al. 2022; Zhao, et al. 2022). Lumen Bioscience has expanded its platform capabilities by developing manufacturing-scale compatible processes to generate a shelf-stable dried spirulina extract containing bioactive protein. The spirulina biomass is inert (nonviable) following the extraction process. Based on recent preclinical data from hamster SARS-CoV-2 challenge studies, we expect that spirulina extract powders containing pathogen neutralizing proteins can serve as an effective antiviral drug. Lumen proposes to intranasally deliver anti-SARS-CoV-2 viral-binding proteins to the upper airway mucosa using a dry powder inhaler. The product objective is to prevent disease in uninfected individuals and potentially block transmission from infected individuals to others (Figure 4-A).

Figure 4-A Product Objective: Prevent disease in uninfected individuals and potentially block transmission from infected individuals to others

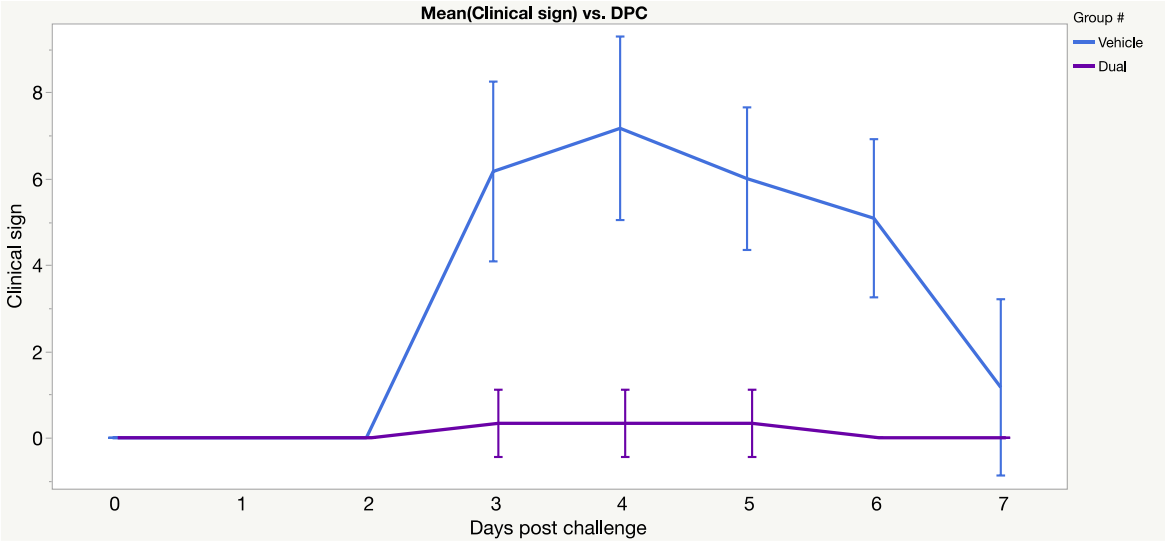


The investigational product, LMN-301, consists of intranasally delivered soluble extract of spirulina (Arthrospira platensis) grown from two separate strains, each of which has been engineered to express intracellularly an antibody-like fusion protein that binds and inhibits SARS-CoV-2. Spirulina was selected as the expression host because of its favourable safety and manufacturing characteristics. The engineered virus-binding proteins are derived in part from the antigen-binding domains of camelid single-domain antibodies (also known as VHHs or nanobodies). LMN-301 will be delivered as a dry powder using a single Unidose (UDS) Power Nasal Spray System device (Aptar, Crystal Lake, IL, USA).

Two *in vivo* hamster SARS-CoV-2 challenge studies were performed using a single VHH (SP1844) contained in the LMN-301 intranasal product to demonstrate safety and efficacy. Due to the difficulty of dry powder delivery in a small rodent model, the dry powder was delivered as a reconstituted slurry.

In the first study, a single pre- or post- treatment with the spirulina product administered intranasally—either before or after SARS CoV-2 exposure— improved clinical outcomes significantly. The dual, two-dose treatment had an even greater effect, appearing to prevent disease completely (Figure 4-B). The dose size was comparable to the dose planned for this Phase 1 trial and was well tolerated in this hamster challenge model. Clinical observations were recorded twice daily throughout the study. No adverse clinical observations were reported that were deemed attributable to vehicle or test item administration.

Figure 4-B Mean clinical sign for vehicle and dual treatment groups



Dual=pre- and post-exposure administration

The second smaller hamster challenge study in the US, had results consistent with the first study. LMN-301 was well tolerated and showed no adverse effects in this second hamster challenge study.

Further details of these studies are provided in the Investigator Brochure.

4.2 Selection of Dose

The amount of powder to be administered is the maximum tolerated amount according to the device manufacturer Aptar.

The dose of LMN-301 selected for use in this clinical study (50 mg total per dose, delivered IN as 25 mg to each nostril) is comparable to the doses that were well tolerated in the hamster challenge studies. In the hamster study, 5 mg dry weight of extract was administered per nare, with each animal receiving 10 mg total dry weight. The estimated nasal surface area of a hamster is 1000 mm2, compared with 18,000 mm2 for humans, resulting in a scaling factor of 18x. A direct scaling of the well-tolerated hamster dose would therefore be 90 mg per nostril or 180 mg total per patient. This would significantly exceed the manufacturer's recommendation for the device. By administering less than 1/3 of the scaled equivalent dose already tested in hamsters, tolerability concerns are not expected.

Both therapeutic proteins in LMN-301 have low potential for systemic exposure and immunogenicity because of:

- their large size, which prevents intact systemic absorption
- the route of administration (intranasal)
- the lack of glycosylation and human Fc domains, which are required for active antibody transport mechanisms.

For further information, please refer to the Investigator Brochure.

4.3 Risk/Benefit Assessment

The potential risks are those associated with phlebotomy and intranasal administration of LMN-301.

Anticipated reactions: Volunteers may experience localized reactions such as sneezing, nasal discharge, nasal tenderness or pain, or nasal irritation post intranasal administration of LMN-301.

Intranasally administered recombinant protein therapeutics have been evaluated in humans since the dawn of the modern biotechnology era. Starting in 1982 with recombinant interferon therapy (Scott et al., 1982), a wide range of therapeutic proteins have been safely tested in humans. As might be expected given what is known about the barrier function of mucosal tissues, across scores of independent clinical trials spanning four decades, none of these report significant adverse events plausibly related to the intranasally administered protein therapeutic (see, e.g., Scott et al., 1982; Higgins et al., 1983; Hayden et al., 1986; Heikkinen et al., 1998; Weltzin et al., 1999). Recent years have also seen an uptick in interest in probiotic therapies—including intranasally administered probiotics (Endam et al., 2021; Lambert et al., 2021; Marchisio et al., 2015; Mårtensson et al., 2017; Tran et al., 2022). Despite such investigational products being neither sterile (by definition) nor axenic, they confirm the intuitive result: mucosally delivered biologics are significantly safer than their injected counterparts.

These general lessons also extend to the particular details of LMN-301's formulation. Antibodies, VHHs, and other similar therapeutic proteins have been orally and intranasally administered in many human clinical trials without reports of SAEs or drug-related AEs (Carlton et al., 2018; Lochhead & Thorne, 2012; Nurbhai et al., 2019; Sarker et al., 2013). The safety, tolerability, and efficacy of intranasally administered therapeutic proteins against SARS-CoV-2 has been demonstrated in humans by at least six independent groups (de Vries et al., 2021; Haga et al., 2021; Huo et al., 2021; Imsuwansri et al., 2022; Nambulli et al., 2021; Song et al., 2023). Remarkably, three of these groups achieved these results using simpler, less potent versions of the VHH antibodies within LMN-301. All were safe and well-tolerated.

This was not unexpected. Intranasal and mucosal delivery of therapeutic proteins has low potential for systemic exposure and immunogenicity (Hickey & Stewart, 2022). Historically, in passive nasal immunizations studies against coxsackie virus, rhinovirus, and respiratory syncytial virus, systemic reactions have not been observed (Buthala Ph.D. et al., 1970; Hayden et al., 1988; Rimensberger & Schaad, 1994). Inhalational administration of ALX-0171, a nanobody directed against respiratory syncytial virus, did not induce systemic reactions in multiple studies in adults, children, and infants (De Bruyn et al., 2015). Recipients of intranasal LMN-301 in this study are healthy volunteers so are not expected to receive any treatment benefit. However, an effective COVID-19 preventative would offer a societal benefit. Considering the overall burden of the disease, the sponsor considers the potential benefits of participation to exceed the risks.

5 STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are provided in Table 5-A below:

Table 5-A LMN-301 COV01 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the safety and tolerability of single and multiple doses of intranasally delivered LMN-301	• Safety and tolerability of single and multiple doses of intranasally administered LMN-301 as measured by: ○ The occurrence of solicited AEs for 28 days after the first dose of LMN-301 ○ The occurrence of unsolicited AE/SAEs for up to 28 days after the first dose of LMN-301 ○ Discontinuation ○ Changes from baseline in vital signs, safety laboratory parameters, ECG parameters and nasal symptoms using the Sino-nasal outcome test
Secondary	
To determine the persistence profile of LMN-301 in the nasal mucosa following single and multiple doses	• Detect the presence of LMN-301 in nasal mucosal lining fluid samples collected from study participants
Exploratory	
To detect the presence of LMN-301 and anti-drug antibodies in serum	• Detection of LMN-301 virus-binding proteins and anti-virus binding protein Immunoglobulin G (IgG) in serum samples

6 STUDY DESIGN

6.1 Overall Design Type and Description

This is a Phase I, open-label single site study of LMN-301 administered intranasally as single or multiple doses in healthy volunteers.

This study will be conducted in two parts.

Study volunteers will be screened for eligibility within 28 days of initiating study drug. Up to 35 eligible volunteers will be enrolled in the study and sequentially assigned to the sentinel cohort (Part A, n=5) or to one of the three multiple-dose cohorts (Part B, n=10/group).

6.2 Part A (Sentinel Cohort)

On Day 1, 5 participants will be administered a single dose of LMN-301 intranasally to each nostril at a fixed dose of 50 mg (25 mg in each nostril) using the Unidose (UDS) Powder Nasal Spray System device (Aptar). Eligible participants will be admitted to the clinic on Day 1 prior to dosing, and will be observed as in-patients for 24 hours following study drug administration. Participants will be discharged on Day 2 and then followed on an outpatient basis for 14 days. Protocol-specified evaluations and procedures will be performed on Days 1-2 and then weekly or bi-weekly. Participants will be required to return to the clinic for an outpatient visit on Day 8. Telephone follow-up will be conducted on Days 3 to 7, with an end of study telephone follow up on Day 14.

There is no safety review committee for this study, however safety and tolerability data collected from the sentinel cohort participants will be reviewed by the principal investigator, the independent medical monitor, and the sponsor medical monitor, to decide whether to move forward with the multiple-dose cohorts (Part B). The discussion will include review of the study and individual stopping rules.

The schedule of assessments (SoA) for the sentinel cohort (Part A) is presented in Table 21-A, with a description of study schedule and procedures provided in Sections 10 and 11.

6.3 Part B (Multiple Dose)

Up to 30 participants will be sequentially assigned to one of three dosing groups (10 participants per group) starting with Group 1. Participants will be administered LMN-301 intranasally to each nostril at a fixed dose of 50 mg (25 mg in each nostril) every third day for 12 days (Group 1), every other day for 12 days (Group 2) or every day for 12 days (Group 3). All study participants will be observed in the clinic for 4 hours after the first dose.

Participants will be monitored for the occurrence of any adverse events (AEs) and serious adverse events (SAEs). Vital signs, physical exams and safety/laboratory testing will be performed on Days 1, 3 or 4, 7 and 14. Participants will use a diary (paper or electronic) to record any symptoms from the first dose through 28 days after the first dose.

Serum will be collected on Days 1 (baseline before dosing and 2 hours after dosing), 3 or 4, 7 and 14 for analysis to detect systemic absorption of virus-binding proteins and anti-drug antibodies (ADA).

Nasal mucosal lining fluid (MLF) samples will be collected using Synthetic Absorptive Matrix (SAM) strips (Nasosorption™ FX·I, Hunt Developments (UK) Ltd, United Kingdom) from all participants on Day 1 (baseline before dosing and 2 hours after dosing), and on Days

3 or 4, 7 and 14. Nasal MLF samples will be sent to Lumen Bioscience (Seattle, WA, USA) for analysis.

The schedule of assessments (SoA) for part B is presented in Table 21-B with a description of the study schedule and procedures provided in Sections 10 and 11.

6.4 Safety Review

6.4.1 Safety Review Committee

There is no safety review committee for this study, however safety and tolerability data collected from the sentinel cohort participants will be reviewed by the principal investigator (PI), the independent medical monitor, and the sponsor medical monitor, either via email or meeting if required. The PI will decide whether to move forward with the multiple-dose cohorts (Part B) taking into account recommendations from the medical monitor and the sponsor medical monitor. The discussion will include review of the study and individual stopping rules.

6.4.2 Dose Stopping Rules

AEs which will prompt stopping the investigational product administration for all subjects and review include:

- Any individual experiencing any SAE considered at least possibly related to the investigational products; or
- If two or more subjects experience the same or similar unanticipated adverse event that is Grade 3 in severity or higher; or
- If the accumulation of SAEs and/or severe AEs collectively raises a safety concern in the opinion of the PI, Medical Monitor, or Sponsor.
- If any individual experiences liver function tests or creatinine increased to 3 times the upper limit of normal; or
- If any individual experiences significant spontaneous bleeding or platelet count < 100 X 10^9/L; or
- If any individual experiences coagulation disorders characterised by prolonged PT; or PTT or abnormal INR greater than 1.5 times the upper limit of normal
- If any individual experiences neutrophil values < 1.0 x 10^9L

The decision to restart the study will be made by consensus of the Independent Medical Monitor, the sponsor's medical expert, and the Principal Investigator. The decision to stop the study will be communicated to the HREC and, similarly, the decision to re-start a study will also be communicated to the HREC.

Administration of the investigational product will be discontinued for any subject that develops:

- A serious adverse event considered at least possibly related to the investigational product; or
- An adverse event that is Grade 3 or higher and considered at least possibly related to the investigational product; or
- The Principal Investigator deems that stopping the investigational product administration is in the best interest of the subject.

6.5 Participant Withdrawal Criteria

Participants will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the PI (or delegate) may discontinue a participant from the study to protect the participant's health. A participant may voluntarily withdraw or be withdrawn from the study for reasons including, but not limited to, the following:

- The need to take medication which may interfere with study measurements.
- Intolerable/unacceptable AEs.
- Positive test for Covid-19
- Noncompliance of the participant with the protocol.
- Withdrawal of consent; or
- If, in the PI's (or delegate's) judgement, it is in the participant's best interest.

The Sponsor will be notified as soon as possible of any participant withdrawals. The date and reasons for withdrawal will be recorded in the eCRF and included in the final clinical study report, along with any AEs and necessary medical treatment (up until the point of study withdrawal).

Any participant who prematurely discontinues study drug, should have, if possible, all scheduled safety assessments performed, including all follow-up visit assessments as scheduled. If a participant withdraws from the study, an attempt should be made to collect all remaining safety samples scheduled for that day.

In the event that a participant is discontinued from the study due to an SAE, the PI (or delegate), or medically trained nominee, will evaluate the urgency of the event. If the situation warrants, the PI (or delegate), or medically trained nominee, will take appropriate diagnostic and therapeutic measures and attempt to notify the sponsor's medical expert. If the situation is not an immediate emergency, the PI (or delegate), or medically trained nominee, at the clinical facility will attempt to contact the sponsor's medical expert for consultation. No medical help, diagnosis, or advice will be withheld from the participant due to an inability to contact the sponsor's medical expert. The participant will be encouraged to remain available for follow-up medical monitoring.

Participants who withdraw from the study prior to treatment will be replaced according to recruitment and enrolment processes outlined in Section 7.3.

6.6 Suspension or Termination of the Study at the Investigational Site

The Sponsor reserves the right to suspend or terminate an investigational site or this clinical study at any time. Reasons will be provided in the event of this happening. Reasons for termination may include, but are not limited to, the following:

- Unacceptable safety and tolerability;
- Serious or persistent noncompliance by the PI with the protocol, clinical research agreement, principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), or applicable regulatory requirements in conducting the study;
- HREC decision to suspend or terminate approval for the PI;
- Regulatory authority request for study suspension or termination;
- Volunteer enrollment is unsatisfactory.

The PI reserves the right to withdraw from the study for safety reasons at any time following

consultation with the Sponsor.

6.7 Treatment Allocation

All study participants who sign an informed consent form at screening will receive a unique sequential number (i.e., a screening number). Participants will be allocated to the next available treatment group in the order they are screened. As this is an open-label study, no randomisation or blinding will occur.

7 PARTICIPANT SELECTION

The screening period starts with the signing of the informed consent. During the screening period, inclusion/exclusion criteria for the study participation will be checked/tested. Subjects who meet all inclusion criteria and do not meet any exclusion criterion will be eligible to be enrolled. Those who are not eligible for enrollment or dosing will be considered as screening failures. Data for screen failure reason, eligibility criteria, and demography will be captured on the appropriate screening and enrolment log.

Assessments may be repeated once, if abnormal values were recorded in the first instance, at the discretion of the PI. Values outside of the ranges specified in the criteria below may be considered acceptable if determined by the Investigator (in conjunction with the study medical monitor) to be not clinically significant (NCS).

Unless specifically defined below, inclusion and exclusion criteria are to be assessed at screening and again on Day 1, prior to dose administration.

7.1 Inclusion Criteria

Individuals must meet all the following criteria to be eligible to participate in this study:

1. Adult (between 18 and 65 years of age) at screening
2. BMI $\geq$ 18.0 and $\leq$ 30.0 kg/m^2, with a maximum body weight of 120 kg at screening.
3. General good health, without significant medical illness or abnormal physical examination findings per investigator discretion.
4. No clinically significant laboratory values at screening for haematology, serum chemistry, coagulation, and urinalysis in the opinion of the Investigator. A repeat test is allowed at the investigator's discretion.
5. Normal electrocardiogram (ECG) with no QTcF prolongation.
6. Must have provided written informed consent to participate in the clinical trial before any study-related activities are carried out and, in the Investigator's opinion, must be able to understand the full nature and purpose of the trial, including possible risks and adverse effects.
7. In the investigator's opinion, participant is willing and able to comply with all study assessments and adhere to the protocol schedule and restrictions.
8. Female volunteers:
    a. Must be of non-child-bearing potential, i.e., surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy at least 6 weeks before the screening visit or postmenopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause (confirmed with FSH testing), or

   b. If of child-bearing potential, must have a negative serum pregnancy test at screening and negative urine pregnancy test before the first study drug administration. They must agree not to attempt to become pregnant, must not donate ova, and must agree to use a highly effective method of contraception from signing consent, throughout the study and for at least 30 days after the last dose of study drug. For contraception guidelines see Appendix 4.
9. Male volunteers must agree not to donate sperm and if engaging in sexual intercourse with a female partner who could become pregnant, must agree to use a condom in addition to having the female partner use a highly effective contraceptive method (Appendix 4) from signing consent, during the study, and at least 90 days after the last dose of study drug.

7.2 Exclusion Criteria

Individuals will be excluded from this study if they meet any of the following criteria:

1. History or presence of clinically significant disease, including (but not limited to) clinically significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, neurological or psychiatric disease, including any acute illness or surgery within the past 3 months prior to screening determined by the PI to be clinically relevant.
2. Known allergy or previous anaphylaxis to any components of the investigational product
3. Allergies, history of allergic disease or chronic respiratory diseases including mild asthma. History of childhood asthma or childhood allergies are not exclusionary.
4. History of nasal or upper respiratory pathology or abnormalities
5. Ongoing, defined as within 30 days of dosing through end of follow-up, usage of nasal spray or nasal drops
6. Treatment with an experimental device or compound within 30 days of the first dose of study drug.
7. Treatment within 30 days of the first dose of the study medication or planned use within the study period with immunomodulator or immunosuppressant agent or medicines (over the counter [OTC], herbal, prescription, or supplement) with significant activity in the respiratory tract.
8. Pregnancy, anticipated pregnancy, or breastfeeding/lactating
9. Alcohol or drug abuse/dependency (defined as more than 10 standard drinks per week or more than 4 standard drinks on any one day, where 1 standard drink is 10 g of pure alcohol) within 3 months prior to screening.
10. Positive urine toxicology screen for drugs of abuse. Repeat testing is allowed at investigator discretion. Tobacco or nicotine consumption is not permitted from screening and until the end of follow-up.
11. Positive alcohol breath test. Repeat test is allowed at investigator discretion.
12. Individuals unable or unwilling to provide adequate informed consent
13. COVID-19 positive
14. Positive test results for active human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibodies at screening.

7.3 Participant Replacement

Replacement of participants is allowed if a participant withdraws or is withdrawn prior to the commencement of dosing.

Participants who withdraw or are withdrawn from the study after administration of the first dose for reasons other than occurrence of an SAE, may be replaced at the discretion of the PI (or delegate) and following consultation with the Sponsor.

Any participants enrolled as replacements will be allocated to the same treatment group as the participant that is being replaced.

8 INVESTIGATIONAL PRODUCT

8.1 Description of Investigational Product

The IP to be used in this clinical study is LMN-301 (active ingredient), formulated as a spray dried powder for intranasal delivery, at a dose of 25 mg intranasally into each nostril (50 mg total dose).

LMN-301 consists of spray-dried extract of biomass of two strains of spirulina (*Arthrospira platensis*) —SP1844 and SP1835—each of which has been engineered to intracellularly express one of the engineered therapeutic antibody-like fusion proteins that binds and inhibits SARS-CoV-2 (pp1116 and pp1107, respectively). The engineered virus-binding proteins are derived in part from the antigen-binding domains of camelid single-domain antibodies (also known as VHHs or nanobodies).

For convenient intranasal delivery, LMN-301 dry powder is prepared by isolating the soluble protein fraction of spirulina expressing the binding protein constructs, diafiltration and buffer exchange to formulate the product with glycine and trehalose, then spray drying. The spray dried final powder will be delivered to the intranasal cavity of patients in the Unidose (UDS) Powder Nasal Spray System device (Aptar, Crystal Lake, IL, USA) (the plume will extend into the entire intranasal cavity). The devices are disposable and for single use. One device per nostril per timepoint will be used.

8.2 Supply, Packaging and Labelling

The study drug, LMN-301, will be supplied by Lumen Bioscience, Inc. (Seattle, WA, USA). LMN-301 doses (25 mg) are packaged into each Aptar Unidose device (Aptar, Crystal Lake, IL) for intranasal administration. The Unidose devices will be individually packaged in labelled mylar bags (2 devices per bag), and labelled appropriately.

The manufacturer will provide the site (or site pharmacy) with a sufficient quantity of study drug (LMN-301) for the conduct of the study. The investigational pharmacy will dispense LMN-301 according to the Pharmacy Manual.

Study drugs will be labelled according to current GMP (cGMP), as adopted in each country/region.

Standard operating procedures will be followed for the receipt, handling and accountability of the study drugs.

Additional details are provided in the study Pharmacy Manual.

8.3 Storage

All investigational products will be kept in a locked area with limited access. Unidose (UDS) Powder Nasal Spray System devices will be provided in labelled mylar bags and should be stored at room temperature, 59-77°F (15-25°C) and protected from moisture, light, and extreme heat during storage. The site must maintain a temperature log for all study drugs held on site, and the Sponsor must be contacted as soon as possible for any temperature excursions.

The investigational product contains no preservatives. Any damaged or used devices should be returned to the investigational pharmacy and discarded using appropriate drug disposal procedures and documented. Two Unidose Powder devices containing the IP will be packaged in each mylar bag with a desiccant packet.

Only participants enrolled in the study may receive the investigational product in accordance with all applicable regulatory requirements. Upon the completion of the study, this material will be subjected to final inspection and reconciliation. At that time, all unused, partially used, and fully used devices along with a packing slip must be destroyed as per the pharmacy manual. Documentation of destruction will be retained by the investigational pharmacy with the study files.

8.4 Investigational Product Dispensing

In accordance with all applicable regulatory requirements and the protocol, only participants enrolled in the study may receive study drug (LMN-301). Only authorised and trained site staff may dispense the study drug.

The PI is responsible for ensuring that all study drugs are dispensed in accordance with the protocol and only to participants enrolled in the study.

Upon receipt of a prescription/authorisation from the Investigator (or delegate), the study pharmacist (or delegate) will dispense the doses of LMN-301.

At the time of dispensing the pharmacist (or delegate) will complete the applicable fields on the label.

8.5 Administration of Investigational Product

A Unidose Nasal Device (Aptar Pharma) will be used to deliver the doses of LMN-301 (Figure 8-A). The Sponsor will provide the Aptar Unidose Nasal Devices pre-filled with LMN-301.

Figure 8-A Unidose Nasal Device

Each Unidose nasal device delivers a dose of 25 mg. Detailed instructions are provided in the study Pharmacy Manual.

The total dose to be delivered will be divided equally across both nostrils, with a total of 1 actuation per nostril required for each dose, i.e., a total dose of 50 mg (See Table 8-A).

All dosing will take place in the clinical facility under the supervision of site staff.

Participants in study Part A (sentinel cohort) will be observed as in-patients for 24 hours after administration of study drug.

Participants in study Part B (multiple dose cohort) will be observed on site for 4 hours after administration of the first dose.

- Participants in Group 1 will return to the site every 3rd day (Days 4, 7 and 10) for dosing and safety monitoring
- Participants in Group 2 will return to the site every 2nd day (Days 3, 5, 7, 9 and 11) for dosing and safety monitoring
- Participants in Group 3 will return to the site daily (Days 2 to 12) for dosing and safety monitoring

Details of dose administration will be recorded in the eCRF.

Table 8-A LMN-301 Dosing of Study Participants in Study Parts A and B

Cohort No.	Number of Participants to be Dosed with LMN-301	Dose delivered per actuation	Number of actuations per nostril (to be administered in each nostril)	Total Fixed Dose	Dosing Frequency	Total number of doses
Part A (Single dose)						
Sentinel cohort	5	25 mg	1	50 mg	Once only	1
Part B (Multiple dose)						
Group 1	10	25 mg	1	50 mg	Every 3rd day, for 12 days	4

Cohort No.	Number of Participants to be Dosed with LMN-301	Dose delivered per actuation	Number of actuations per nostril (to be administered in each nostril)	Total Fixed Dose	Dosing Frequency	Total number of doses
Group 2	10	25 mg	1	50 mg	Every 2nd day, for 12 days	6
Group 3	10	25 mg	1	50 mg	Daily, for 12 days	12

8.6 Accountability of Investigational Product Supplies

All study drug supplied is for use only in this clinical study and should not be used for any other purpose.

The PI (or delegate) is responsible for study drug accountability, reconciliation, and record maintenance at the clinical facility. In accordance with all applicable regulatory requirements, the PI or designated trained site staff must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received from the Sponsor (or designee) and the amount dispensed to, administered to, and returned by participants, as applicable. The shipment/receipt records as well as records of dispensing, administration and return will be verified by a second member of the site staff. The PI (or designated trained site staff) is responsible for assuring the retrieval of all left-over study drug supplies following administration to participants.

Used packages of the study drug will be retained and sequestered per participant and made available to the CRA during study drug reconciliation.

When requested in writing by the Sponsor and following review and reconciliation of study drug accountability, unused study drug supplies may be returned to the Sponsor or destroyed by the PI (or delegate), provided destruction does not expose humans to risks from the study drugs. Records shall be maintained of the return or destruction of the study drug materials. These records must show the identification and quantity of each unit returned or disposed of, the method of destruction (taking into account the requirements of local law), and the person who returned or disposed of the study drug materials. Such records must be submitted to the Sponsor.

9 PRIOR/CONCOMITANT MEDICATIONS AND OTHER RESTRICTIONS

9.1 Prior and Concomitant Medications

Subjects will be monitored throughout the study for the use of concomitant medications. A concomitant medication is defined as any non-study medication taken after the first dose of study drug (including where these medications were commenced prior to first dose administration and continued after first dose administration) through to the final follow-up visit. A prior medication is defined as any non-study medication taken within 28 days prior to screening but ceased prior to the first dose of study drug.

For both study parts, only concomitant medications approved by the study physician should be used during the study. Subjects taking regular medication (e.g., contraceptives) prior to enrolment will be allowed to continue unless it is specifically excluded as part of the inclusion/exclusion criteria. Subjects requiring non-approved or excluded medications will not be eligible for enrolment. Approved medications that were being taken prior to and during the trial will be documented.

Use of the following medications is prohibited during the study:

- Ongoing (defined as within 30 days of the first dose through to the end of follow-up) use of nasal spray or nasal drops
- Treatment with an experimental device or compound within 30 days of the first dose of study drug
- Treatment within 30 days of the first dose of the study medication or planned use within the study period with an immunomodulator or immunosuppressant agent or medicines (over the counter [OTC], herbal, prescription, or supplement) with significant activity in the respiratory tract.

If the need for concomitant medication arises to treat an AE, the Investigator should make decisions on medication use based on the participant and clinical factors.

If a concomitant medication is started during the study, a decision whether the participant may continue in the study will be made by the PI (or delegate), in consultation with the sponsor's medical expert.

Any non-study medication that is taken by or administered to a participant from 28 days prior to screening through their final study visit must be recorded in the eCRF. The entry must include the medication name, indication, dose, dose regimen, route of administration, and start/stop dates.

9.2 Tobacco and Alcohol

Participants must have a negative drugs of abuse urine test and alcohol breath test at Screening and on Day 1 prior to dosing, and must abstain from recreational drug use throughout the study.

Use of tobacco products or nicotine-containing products (including smoking cessation aids such as gum or patches), are prohibited from Screening and until their last study visit.

9.3 Contraception

Female participants of childbearing potential, must agree not to attempt to become pregnant,

must not donate ova, and if not exclusively in a same-sex relationship, use adequate contraception (Appendix 4) from signing the consent form until at least 30 days after the last dose of study drug. Additionally, female participants of childbearing potential must use adequate contraception for at least 1 month prior to screening.

Male participants, must agree not to donate sperm and if engaging in sexual intercourse with a female partner who could become pregnant, must agree to use a condom plus a have the female partner use a highly effective contraceptive method (Appendix 4) from signing the consent form until at least 90 days after the last dose of study drug.

9.4 Fasting

There are no fasting requirements in this study. Standard meals will be provided to participants during the confinement period and also during extended outpatient visits, as appropriate.

9.5 Blood Donation

All study participants will be advised not to donate blood or blood products (> 470 mL) within 3 months prior to screening and for 3 months following the final follow-up visit.

10 STUDY SCHEDULE

As presented in the study SoA (refer to Appendix 1, Appendix 2 and Appendix 3), Screening, Treatment, Follow-up and End of study assessments will be performed for all participants.

10.1 Screening

All participants (Part A and Part B) will be screened for eligibility within 28 days of the first dose of study drug. The following procedures will be performed at screening:

- Informed consent
- Inclusion/exclusion criteria
- Demographics (age, race, sex, ethnicity)
- Height and weight
- Medical/surgical history, comorbidities
- Prior and concomitant medications
- Serum pregnancy test (females of child-bearing potential only)
- Collect blood for follicle-stimulating hormone levels (post-menopausal women only)
- Urine tox screen for drugs of abuse
- Alcohol breath test
- Physical examination
- Vital signs (systolic and diastolic blood pressure, pulse rate, oral temperature, respiration rate)
- Twelve-lead ECG
- Collect urine for urinalysis
- Collect whole blood for hematology
- Collect serum for chemistry
- Collect blood for PT, APTT, INR
- Collect blood for viral serology testing (HIV antibody, HBsAg, HCV)
- Perform Sino-Nasal Outcome Test
- COVID-19 RAT test

10.2 Part A Sentinel Cohort (open-label, one fixed dose)

In Part A, 5 sentinel participants will be observed for 24 hours as inpatients, and then followed for 14 days. Protocol-specified evaluations and procedures will be performed on Day 1-2 and weekly or bi-weekly as outlined below and in the SoA (Appendix 1).

10.2.1 Day 1 Inpatient

Eligible volunteers will be admitted to the research unit. The following procedures will take place on Day 1:

- Record concomitant medications before and after drug administration
- Review inclusion/exclusion criteria before dosing
- Urine pregnancy test (females of child-bearing potential only) before dosing
- COVID-19 RAT test before dosing
- Urine tox screen for drugs of abuse before dosing
- Alcohol breath test before dosing
- Collect whole blood for hematology before dosing
- Collect serum for chemistry before dosing

- Collect blood for PT, APTT INR before dosing
- Perform a targeted physical examination before dosing
- Perform a nasal examination within 1 hour before and 3 hours after drug administration
- Vital signs within 2 hours before and at 30 minutes, 1 hour and 4 hours after drug administration
- Collect serum for drug detection before and 2-hours after drug administration
- Collect serum for anti-drug antibodies before and 2 hours after drug administration
- Collect nasal mucosal lining fluid (MLF) samples before and 2-hours after drug administration
- Administer study drug by intranasal delivery to each nostril using a unidose powder device
- Perform Sino-Nasal Outcome Test at 2 hours after drug administration
- Record solicited AEs (stuffy nose, runny nose, sneezing, nasal irritation, nasal tenderness/pain, loss of smell, sore throat scratchy throat, cough) and unsolicited AEs/SAEs
- Participants will be provided with a diary (paper or electronic) to record any solicited and/or unsolicited AEs daily, and to record concomitant medication usage.

10.2.2 Day 2 Inpatient

- Perform a targeted physical examination
- Vital signs
- Collect whole blood for hematology
- Collect serum for chemistry
- Collect blood for PT, APTT, INR
- Collect serum for drug detection
- Collect serum for anti-drug antibodies
- Collect nasal mucosal lining fluid (MLF) sample
- Record solicited AEs and unsolicited AEs/SAEs
- Review diary
- Record concomitant medications
- Discharge participants

10.2.3 Days 3-7

Research staff will perform daily telephone calls to the patient during this period to assess the emergence of AEs (solicited and unsolicited) and concomitant medication usage (recorded in the diary).

10.2.4 Day 8 Outpatient Visit

- Perform a targeted physical examination
- Vital signs
- Collect whole blood for hematology
- Collect serum for chemistry
- Collect blood for PT, APTT, INR
- Collect serum for drug detection
- Collect serum for anti-drug antibodies

- Collect nasal mucosal lining fluid (MLF) sample
- Perform Sino-Nasal Outcome Test
- Review diary
- Record solicited AEs and unsolicited AEs/SAEs
- Record concomitant medications

10.2.5 Day 14 Outpatient Visit (End of Study)

- Perform a targeted physical examination
- Vital signs
- Record solicited AEs and unsolicited AEs/SAEs
- Record concomitant medications
- Twelve-lead ECG
- Urine pregnancy test (WOCBP only)
- Collect whole blood for hematology
- Collect serum for chemistry
- Collect blood for PT, APTT, INR
- Urine collection for urinalysis
- Site staff to collect diary

10.3 Part B Multi-Dose Cohort (Multi-dose, Open-label)

The safety data from the sentinel cohort will be reviewed by the principal investigator, the medical monitor, and the sponsor study physician to make a decision whether to move forward with the multiple dose cohorts (Part B). As part of the decision process, the principal investigator, the independent medical monitor, and the sponsor study physician will consider the study and individual stopping rules (see Section 6.4.2).

In Part B, 30 participants will be administered LMN-301 (n=10/group) intranasally into each nostril every third day for 12 days (Group 1), every other day for 12 days (Group 2) or every day for 12 days (Group 3).

Participants will be observed in the clinic for 4 hours after the first dose. Protocol-specified evaluations and procedures will be performed as outlined below and in the SoA (Appendix 1).

Nasal mucosal lining fluid (MLF) samples will be collected from all participants on Day 1 (baseline before dosing and 2 hours after dosing), and on Days 3 or 4, 7 and 14. Nasal MLF samples will be sent to Lumen Bioscience for analysis.

Participants will use a diary to record concomitant medication usage and any symptoms from the first dose through Day 28 after the first dose.

10.3.1 Day 1

Eligible volunteers will come into the clinic on Day 1 and the following procedures will take place on Day 1:

- Record concomitant medications before and after dosing
- Review inclusion/exclusion criteria before dosing
- Perform urine pregnancy test before dosing
- Urine tox screen for drugs of abuse

- Perform alcohol breath test
- COVID-19 RAT test before dosing
- Urine pregnancy test before dosing (females of child-bearing potential only)
- Collect whole blood for hematology before dosing
- Collect serum for chemistry before dosing
- Collect blood for PT, APTT, INR before dosing
- Perform a targeted physical examination within 1 hour before drug administration
- Perform a nasal examination within 1 hour before and 3 hours after drug administration
- Vital signs within 1 hour before and at 15 minutes, 30 minutes, 1 hour and 4 hours after drug administration
- Collect serum for drug concentration before and 2 hours after drug administration
- Collect serum for anti-drug antibodies before and 2 hours after drug administration
- Collect nasal MLF sample before drug administration and 2 hours after dosing
- Participants in all dosing groups will be administered study drug by intranasal delivery into each nostril using the Aptar Unidose device.
- Perform Sino-Nasal Outcome Test at 2 hours after drug administration
- Participants will be observed in the clinic for 4 hours after dosing.
- Record solicited AEs and unsolicited AEs/SAEs
- Participants will be provided with a diary to record any solicited and/or unsolicited AEs and concomitant medication usage daily, from Days 1-28 (inclusive).

10.3.2 Day 2-12 Treatment Phase and Clinic Visits

Group 1

- Participants will attend the clinic every third day (Days 4, 7 and 10).
- A targeted physical exam (See Section 11.11) will be performed within 1 hour prior to dose administration on Days 4, 7 and 10
- Vital signs will be performed within 1 hour prior to dose administration on Days 4, 7 and 10
- Blood collection for hematology and coagulation markers (PT, APTT, INR), collection of serum for chemistry will be performed within 1 hour prior to dose administration on Days 4 and 7
- Blood samples for investigational drug detection and anti-drug antibodies will be collected any time prior to drug administration on Days 4 and 7.
- Study drug will be administered under supervision in the clinic by intranasal delivery into each nostril every third day (Days 4, 7 and 10) using the Aptar Unidose device.
- A nasal examination will be performed 3 hours after drug administration on Day 4, 7 and 10
- A COVID-19 RAT test will be performed before dosing on Day 4, 7 and 10.
- A Sino-Nasal Outcome Test on will be performed on Day 7 at 2 hours after drug administration.
- Intranasal MLF samples will be collected prior to dosing on Day 4 and Day 7.
- Subject diaries will be reviewed by study staff at each clinic visit.
- Record solicited AEs and unsolicited AEs/SAEs daily
- Record concomitant medication use daily

Group 2

Participants will attend the clinic every other day (Days 3, 5, 7, 9 and 11).

- A targeted physical exam will be performed within 1 hour prior to dosing on Days 3, 7 and 11.
- Vital signs will be assessed within 1 hour prior to dosing on Days 3, 7 and 11.
- Blood collection for hematology and coagulation markers (PT, APTT, INR), collection of serum for chemistry within 1 hour prior to dosing on Days 3 and 7.
- Blood samples for investigational drug detection and anti-drug antibodies will be collected on Day 3 and Day 7, any time prior to drug administration.
- Study drug will be administered under supervision in the clinic by intranasal delivery into each nostril every other day (Days 3, 5, 7, 9 and 11) using the Aptar Unidose device.
- A nasal examination will be performed 3 hours after drug administration on Day 3, 7 and 11.
- A COVID-19 RAT test will be performed before dosing on Day 3, 7 and 11.
- A Sino-Nasal Outcome Test on will be performed on Day 7 at 2 hours (±15 mins) post-dose.
- Intranasal MLF samples will be collected prior to dosing on Day 3 and Day 7.
- Subject diaries will be reviewed by study staff at each clinic visit.
- Record solicited AEs and unsolicited AEs/SAEs daily
- Record concomitant medication use daily

Group 3

- Participants will attend the clinic daily (Days 2-12).
- A targeted physical exam will be performed within 1 hour prior to dosing on Days 3, 7 and 11.
- Vital signs will be assessed within 1 hour prior to dosing on Days 3, 7 and 11
- Blood collection for hematology and coagulation markers (PT, APTT, INR), collection of serum for chemistry within 1 hour prior to dosing on Days 3 and 7.
- Blood samples for investigational drug detection and anti-drug antibodies will be collected on Day 3 and Day 7, any time prior to drug administration.
- Study drug will be administered under supervision in the clinic by intranasal delivery into each nostril daily (Days 2-12) using the Aptar Unidose device.
- A nasal examination will be performed 3 hours after drug administration on Day 3, 7 and 11.
- A COVID-19 RAT test will be performed before dosing on Day 3, 7 and 11.
- A Sino-Nasal Outcome Test on will be performed on Day 7 at 2 hours (±15 mins) post-dose.
- Intranasal MLF samples will be collected prior to dosing on Day 3 and Day 7.
- Subject diaries will be reviewed by study staff at each clinic visit.
- Record solicited AEs and unsolicited AEs/SAEs daily
- Record concomitant medication use daily

10.3.3 Day 14 Follow-up visit

Participants will attend the research unit on Day 14 and the following procedures will take place:

- Recording concomitant medications

- A COVID-19 RAT test
- Targeted physical examination
- Vital signs
- Collect whole blood for hematology
- Collect serum for chemistry
- Collect blood for PT, APTT, INR
- Collect serum for drug concentrations
- Collect serum for anti-drug antibodies
- Collect nasal mucosal lining fluid (MLF) sample
- Perform Sino-Nasal Outcome Test
- Review diary
- Record AEs/SAEs

10.3.4 Days 15-17

Solicited and unsolicited AEs/SAEs and concomitant medications will be recorded daily using the participant diary

10.3.5 Day 28 End of Study Visit

Participants will come into the research unit on Day 28 and the following procedures will take place:

- Recording concomitant medications
- Vital signs
- Twelve-lead ECG
- Perform Sino-Nasal Outcome Test
- Collect whole blood for hematology
- Collect serum for chemistry
- Collect blood for PT, APTT, INR
- Collect urine for urinalysis
- Record AEs/SAEs
- Review and collect diary
- Urine pregnancy test (females of child-bearing potential only)

11 STUDY PROCEDURES

For the exact timing of each procedure, please refer to the study SoA (refer to Appendix 1, Appendix 2 and Appendix 3). Clinical staff are required to perform assessments at the nominated timepoints within the time windows indicated in the SoA. Actual times of procedures for each participant may vary depending on scheduling and will be recorded in the eCRF. In the event of multiple procedures scheduled at the same time, the order, where possible, will be (1) vital signs, (2) 12-lead ECG, (3) PK/PDc sampling (4) safety laboratory blood sampling (5) all other procedures.

Where required, the timing of post-dose procedures will be in reference to administration of the last actuation completed.

11.1 Informed Consent

The Information and Informed Consent Form (ICF) will be provided to participants at

Screening and signed prior to any study procedures being performed. Investigators at each site are responsible for maintaining a record of all participants consented, including both those who enter the study and those who do not.

11.2 Demographics

Demographic information collected will include age, sex, race, and ethnicity. Where local regulations do not permit certain demographic data to be collected, collection of those data will not be required.

11.3 Medical and Surgical History

A full medical history will be obtained at Screening (to be updated on Day 1, prior to dose administration), including medication history and drug allergies. Medical history can be obtained through participant interview and medical records.

All findings will be recorded on the Medical History eCRF.

11.4 Prior and Concomitant Medications and Therapies

All medications and therapies administered to participants between signing the ICF and the final follow up visit will be recorded in the participant's eCRF. The name, dose, route of administration, dosing schedule, indication and start and stop dates of all medications and therapies must be recorded. Dates of changes to medications (commencement, cessation and/or alteration in dose or schedule) should also be recorded. Medications include prescription and over the counter medications (including herbal products, vitamins, nutritional supplements). For participants entering on a stable dose of permitted medication, any change in dose should also be recorded.

11.5 Height and Weight

Body height (centimetres) and weight (kilograms) will be measured, and body mass index (BMI) will be calculated. Height should ideally be measured on a wall-mounted stadiometer. Weight should be measured in light-weight clothing, without shoes.

11.6 COVID-19 Rapid Antigen Test

A COVID-19 rapid antigen test (RAT) will be performed at the timepoints indicated in the schedule of assessments. Participants who return a positive result will be withdrawn from the study.

11.7 Follicle-Stimulating Hormone

Female participants who report as postmenopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause) will have a serum FSH test at screening. If serum FSH levels are below the cut-off limit as defined by the local testing laboratory, participants will be considered to be of childbearing potential and will be required to use appropriate contraception for the duration of the study.

11.8 Pregnancy Test

Female participants of child-bearing potential will have a serum hCG pregnancy test during Screening. A urine hCG pregnancy test will be conducted on Day 1 as per the SoA. If any of

the urine hCG tests are positive, pregnancy will be confirmed by a serum hCG test. In instances of a positive pregnancy result at any time point, the participant will be withdrawn from the study. Participants withdrawn from the study due to pregnancy may be replaced at the discretion of the PI. Refer to Section 12.7 for pregnancy reporting guidelines.

11.9 Serology

HIV antibody, HBsAg, and HCV antibody will be measured at screening. Participants with a positive result will not be eligible to participate in the study. Investigators must ensure compliance with local governing legislation and reporting requirements associated with communicable diseases.

11.10 Clinical Laboratory Assessments

Blood samples will be collected for haematology, clinical chemistry and coagulation safety assessments; urine samples will be collected for urinalysis, and urine drugs of abuse testing. An alcohol breath test will be performed as indicated in the schedule of assessment for each study part.

Tests performed by the local laboratory are described in Appendix 5. All abnormal assessments assessed as clinically significant (CS) by the PI will be repeated. Abnormal assessments that are not CS may be repeated at discretion of the PI. Note: Any deviation in laboratory values that are confirmed on re-examination to be CS and (in the opinion of the PI or medically qualified nominee) would jeopardise the safety of the participant or impact on the validity of the study results), will result in exclusion/withdrawal of that participant.

All safety laboratory assessments will be assessed by a certified local laboratory, using that laboratory's normal ranges. The Investigator must review the laboratory report, document this review, and record any CS changes occurring during the study in the AE section of the eCRF.

11.11 Physical Examination

Screening physical examinations will include, at a minimum, assessment of the following: general appearance, head, ears, eyes, nose and throat, neck (including thyroid and lymph nodes), respiratory system, cardiovascular system, gastrointestinal system, renal system, neurological system, musculoskeletal system, skin, and any other focused assessments suggested by the presence of specific symptoms.

Targeted physical examination will include general appearance, head, ears, eyes, nose and throat, respiratory system and any other focused assessments suggested by the presence of specific symptoms.

All physical examinations will be conducted by a licensed physician within the time windows specified in the SoA. Physical examinations may also be performed at various unscheduled timepoints if deemed necessary by the Investigator.

All CS findings post-dose will be recorded as AEs.

11.12 Nasal Examination

A macroscopic nasal examination will be performed by conventional anterior rhinoscopy with otoscope with attached otic speculum to assess swelling of the mucosa, erythema, and

secretions at the time of physical examination, at time points specified in the Schedule of Assessments (Appendix 21.1).

All events will be graded for severity as mild, moderate, or severe in the opinion of the investigator (or delegate) (Section 12.2.112.2.1) and recorded as AEs.

11.13 Vital Signs

Vital signs assessments will include systolic and diastolic blood pressure, pulse rate, respiratory rate (RR), and oral temperature. Participants should be resting in a supine/semi-supine position for at least 5 minutes prior to and during vital signs measurements.

Vital signs assessments may be repeated once, if abnormal values (outside of site's normal ranges) were recorded in the first instance, at the discretion of the PI (or delegate).

All CS findings post-dose will be recorded as AEs.

Site normal vital signs ranges are as follows:

- Temperature: ≥35.5 °C to ≤37.7 °C
- Pulse Rate: ≥45 bpm to ≤100 bpm
- Respiratory Rate: ≥12 to ≤22 breaths/min
- Systolic Blood Pressure: ≥90 mmHg to ≤160 mmHg
- Diastolic Blood Pressure: ≥50 mmHg to ≤95 mmHg

11.14 Electrocardiogram

12-lead ECG will be performed at Screening, and at End of Study for both study parts. At each protocol scheduled timepoint, ECGs will be performed in triplicate with each replicate separated by at least 1 minute and the full set of triplicates completed within 5 minutes. The mean value for the triplicate will be utilised. Each ECG will be conducted in a supine (or semi-supine) position after the participant has been resting for at least 5 minutes in a quiet setting without distractions (e.g., television, mobile phones).

Site normal ranges for ECG parameters are as follows:

- HR: 45 bpm to 100 bpm
- PR: ≥120 msec to ≤220 msec
- QRS: <120 msec
- QTcB & QTcF: ≤470 msec (females) or ≤450 msec (males)

ECGs will be interpreted, signed, and dated by the PI (or delegate). The ECGs will be classified as normal, abnormal NCS, or abnormal clinically significant. In addition, ECG parameters of ventricular HR, PR interval, QRS duration, QTcB and QTcF will be noted on the eCRF.

Abnormal ECGs that are clinically significant will be repeated. In the case of evident bad quality (e.g., muscle tremor) of the tracing, an ECG will be repeated. Abnormal ECGs that are NCS may be repeated in at the Investigator's discretion. Repeat assessments will be performed in triplicate.

Additional ECGs may be performed at any time during the study as required, at the discretion of the PI (or designee).

All CS findings post-dose will be recorded as AEs.

11.15 Nasal Symptoms by Sino-Nasal Outcome Test

Nasal symptoms and social/emotional consequences will be assessed using the Sino-nasal outcome test (SNOT-22) at different timepoints, as presented in the SoA (Appendix 21.121.1). Participants will be asked to rate their experience of each of 22 listed symptoms on a scale of 0-5 based on symptoms over the preceding 2 weeks. The rating scale is as shown below:

0 = No Problem

1 = Very Mild Problem

2 = Mild or slight Problem

3 = Moderate Problem

4 = Severe Problem

5 = Problem as bad as it can be

Participants will also be asked to identify up to 5 of the most important issues affecting them, from the list of 22 symptoms.

11.16 Study Diary

Participants will be provided with a study diary on Day 1 to record any solicited and/or unsolicited AEs, and to record concomitant medication usage. Participants will be instructed on use of the diary by site staff during in-person visits.

11.17 Pharmacokinetic Assessments

11.17.1 Blood

Whole blood samples will be collected and processed to obtain serum for the determination of LMN-301 levels on Days 1 (pre- and post-dose), 2 and 8 for the sentinel cohort and on Days 1 (pre- and post dose), 3 or 4, 7 and 14 for the multi-dose cohort. Serum samples will be stored at -80°C until shipped to Lumen Bioscience (Seattle, USA) for subsequent processing and analysis. With the participant's approval, de-identified leftover samples may be stored at Lumen Bioscience indefinitely and used for future research studies related to the development of LMN-301. This future research will not include genomic sequencing. Detailed instructions for the collection, processing, and shipment of samples for LMN-301 PK will be described in the study Laboratory Manual.

11.17.2 Nasal Secretions

Nasal mucosal lining fluid (MLF) samples will be collected on Days 1 (pre- and post-dose), 2 and 8 for the sentinel cohort and on Days 1 (pre-and post-dose), 3 or 4, 7 and 14 for the multi-dose cohort. Sampling will alternate between right and left nostrils during sequential sample collection time points.

MLF samples will be collected using the Nasosorption™ FX·I device (Hunt Developments

(UK), United Kingdom). This device consists of a synthetic absorptive matrix (SAM™) swab to absorb MLF from the mucosa within the nose. MLF will be collected by research staff inserting the swab into the participant's nasal cavity for a period of 60±10 seconds in order to obtain the sample. Samples will be processed and stored, in accordance with the instructions provided in the study Laboratory Manual, as soon as possible following collection. Samples will be shipped to Lumen Bioscience (Seattle, USA) for subsequent processing and analysis to determine the levels of drug product in the MLF. With the participant's approval, de-identified leftover samples may be stored at Lumen Bioscience indefinitely and used for future research studies related to the development of LMN-301. Detailed instructions for the collection, processing, storage and shipment of MLF samples for LMN-301 will be described in the study Laboratory Manual.

11.18 Immunogenicity Assessments

Serum for determination of the presence of anti-LMN-301 antibodies will be collected on Days 1 (pre- and post-dose), 2 and 8 for the sentinel cohort and on Days 1 (pre-and post-dose), 3 or 4, 7 and 14 for the multi-dose cohort. If anti-drug antibodies are confirmed, additional testing on the samples may be performed (e.g., titer and neutralizing antibodies) to further understand the process.

Serum samples will be stored at -80°C until shipped to Lumen Bioscience (Seattle, USA) for subsequent processing and analysis. With the participant's approval, de-identified leftover samples may be stored at Lumen Bioscience indefinitely and used for future research studies related to the development of LMN-301. Detailed instructions for the collection, processing, and shipment of samples for immunogenicity analysis will be described in the study Laboratory Manual.

11.19 Blood Sample Volumes

The following tables contain the approximate blood volumes to be collected per participant throughout the study. The final blood volumes required for each sample type will be documented in the study Laboratory Manual.

Additional blood samples may be collected from a participant at any time throughout the study, if required for safety reasons.

Table 11-A Approximate Blood Sample Volumes Collected Per Participant (Part 1, Single Dose) - Individual

Sample Type	Approximate Blood Volume Per Sample	Number of Timepoints	Approximate Total Volume
Haematology	4 mL	4	16 mL
Serum chemistry	9 mL	4	36 mL
Coagulation	3 mL	4	12 mL
Serology	9 mL	1	9 mL
Serum Pregnancy	Evaluated from serum chemistry blood sample tube, where applicable.		
FSH levels			

Sample Type	Approximate Blood Volume Per Sample	Number of Timepoints	Approximate Total Volume
PK	4 mL	4	16 mL
Immunogenicity	4 mL	4	16 mL
Canula discard	2 mL	4	8 mL
Total approximate volume per participant			113 mL

Abbreviations: FSH = follicle-stimulating hormone; PK = pharmacokinetics
Note: volumes are approximate. Final blood volumes will be documented in the study laboratory manual.

Table 11-B Approximate Blood Sample Volumes Collected Per Participant (Part 2, Multiple Dose)

Sample Type	Blood Volume Per Sample	Number of Timepoints	Total Volume
Haematology	4 mL	6	24 mL
Serum chemistry	9 mL	6	54 mL
Coagulation	3 mL	6	18 mL
Serology	9 mL	1	9 mL
Serum Pregnancy	Evaluated from serum chemistry blood sample tube, where applicable.		
FSH levels			
PK	4 mL	5	20 mL
Immunogenicity	4 mL	5	20 mL
Canula discard	2 mL	5	10 mL
Total approximate volume per participant			155 mL

Abbreviations: FSH = follicle-stimulating hormone; PK = pharmacokinetics
Note: volumes are approximate. Final blood volumes will be documented in the study laboratory manual.

12 ASSESSMENT AND MANAGEMENT OF ADVERSE EVENTS

12.1 Adverse Event Definitions

An **AE** is any untoward medical occurrence in a patient or clinical study participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An **SAE** is any AE that at any dose:

- Results in death.
- Is life-threatening.
  Note: the term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death, if it were more severe).
- Requires inpatient hospitalisation or prolongation of an existing hospitalisation.
  Note: only hospitalisations that are longer than expected based on Investigator judgement, will be considered prolonged hospitalisations.
- Results in persistent or significant disability/incapacity.
  Note: results in a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
  Note: a congenital anomaly/birth defect that occurs in the offspring of a participant exposed to the IP.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that may not be immediately life threatening or result in death or hospitalisation but might jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

A **suspected unexpected serious adverse reaction (SUSAR)**: An AE that meets all the following criteria:

- Is serious
- There is a least a reasonable possibility of a causal relationship between the event and the investigational product
- Is considered unexpected (i.e., the event is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed). "Unexpected" as used in this definition, also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

Abnormal laboratory findings (e.g., serum chemistry, haematology, coagulation, and urinalysis) **or other abnormal assessments** (e.g., vital signs, and physical examination

findings) that are judged by the PI as clinically significant (CS) will be recorded as AEs or SAEs if they meet the definitions stated above. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected after the first administration of the study drug or are present at baseline and significantly worsen following administration of the study drug will be reported as AEs or SAEs. The PI will exercise his/her medical and scientific judgement in deciding whether an abnormal laboratory finding, or other abnormal assessment, is CS.

12.2 Evaluating Adverse Events and Serious Adverse Events

12.2.1 Assessment of Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study. The assessment will be based on the Investigator's clinical judgment. The severity of each AE and SAE will be graded using the most current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) 5-point scale (Table 12-A).

Table 12-A NCI-CTCAE 5-point Scale for Grading the Intensity of Each AE and SAE

Grade		Definition
I	Mild	Asymptomatic or mild symptoms: clinical or diagnostic observations only; intervention not indicated.
II	Moderate	Minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.
III	Severe	Severe or medically significant but not immediately life-threatening: hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL.
IV	Life-threatening	Life-threatening consequences: urgent intervention indicated.
V	Death	Death related to AE.

Abbreviations: ADL = activities of daily living; AE = adverse event.

If an AE/SAE has multiple aspects (symptoms), the aspect with the highest severity will be graded.

The term severe is a measure of severity. Thus, a severe AE is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

12.2.2 Assessment of Causality

The Investigator will make an assessment as to the relationship between study drug and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine whether or not the AE/SAE is causally related to the study drug. Alternative causes, such as natural history of any underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug will be considered and investigated. The Investigator will also consult the Investigator's Brochure in the determination of his/her assessment.

The causal relationship of the study drug to an AE/SAE will be rated according to the following 2-point scale Table 12-B.

Table 12-B Categories for Assessing Relationship of an Adverse Event to Study Drug

Causal Relationship	Definition
Not related	Temporal association with study drug administration is lacking or other causative factors (e.g., participant's clinical state or environmental factors or other therapies administered) more likely explain the event.
Related	There is a reasonable temporal association with administration of study drug or the event is more likely explained by the investigational product than by another cause (i.e., the AE shows a pattern of response consistent with previous knowledge of the study drug).

The causality assessment is one of the criteria used when determining regulatory reporting requirements, therefore, the Investigator must make an assessment of causality based on all available information for every event and prior to transmission of an SAE Form to the Sponsor. The Investigator may change his/her opinion regarding causality in light of follow-up information and amend the SAE Form and the eCRF accordingly.

12.3 Procedures and Time Period for Detecting Adverse Events

The Investigator or designee is responsible for detection, recording and reporting of events that meet the criteria and definition of AEs.

As a consistent method of soliciting AEs, the participant shall be asked a nonleading question such as: "How do you feel?".

The presence or absence following 'solicited AEs' will be assessed by direct questioning:

- stuffy nose
- runny nose
- sneezing
- nasal irritation
- nasal tenderness/ pain
- loss of smell
- sore throat/ scratchy throat
- cough

Detection and recording of study related AEs and SAEs extends from the signing of the consent form until completion of the last study related procedure (including follow-up for safety assessments). Any AE reported or observed at or after the start of dosing with study drug will be recorded as a treatment-emergent AE (TEAE) or SAE.

Any pre-existing conditions or signs and/or symptoms present in a participant prior to the start of the study (i.e., before informed consent), should be recorded as medical history. In addition, any change in health status that is reported or observed after informed consent but prior to starting study drug and is deemed by the study Investigator to be "not related" to study procedures, will be documented as medical history.

A post-study AE/SAE is defined as any event that occurs outside of the nominal AE/SAE study detection period. Investigators are not obligated to actively seek AEs/SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has completed the study and he/she considers the event reasonably related to the investigational product, the Investigator will promptly notify the Sponsor.

Participants must be provided with an "Emergency Wallet Card" indicating the name of the investigational product, the study number, the Investigator's name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

12.4 Recording of Adverse Events and Serious Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded in the eCRF using medical terminology in the eCRF and/or other sources. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion may be reported as "upper respiratory infection"). Investigators must record in the eCRF the date of onset of the event, their opinion concerning the relationship of the event to study drug, severity of the event, whether the event is serious or nonserious, actions taken to manage the event, the outcome of the event, and date of resolution where applicable.

Any change to the severity of an AE must be recorded as a separate AE, ensuring that the end date and time of the preceding AE matches the start date and time of the subsequent AE, so that the overall duration of the AE is continuous.

12.5 Reporting of Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

In accordance with ICH guidelines for GCP, a copy of the written report of any SAEs should promptly be sent to the study Sponsor. The Investigator must notify Sponsor and Sponsor's designated study safety officer within 24 hours of becoming aware of the occurrence of an SAE.

Information regarding SAEs will be transmitted to the Sponsor and Sponsor's designated study safety officer using an SAE form as described in the study SAE Report Form Completion Guidelines. The SAE form must be completed and signed by a member of the investigational staff and transmitted to the Sponsor and Sponsor's designated study safety officer within 24 hours (Table 12-C). New or updated information on the SAE will be recorded on a new SAE form and sent to the Sponsor and Sponsor's designated study safety officer within 24 hours of the information being available. The initial and follow-up reports of an SAE should be made by e-mail.

Table 12-C Contact Details for Transmission of Serious Adverse Event Reporting Forms

Sponsor	Sponsor Designated Safety Officer
Name: Lumen Drug Safety Email: Safety@lumen.bio	Name: Avance Safety Phone: +61 478 034 138 Email: safety@avancecro.com

The Investigator must also report SAEs to the appropriate HREC that approved the protocol

according to their requirements. All SAEs will be reported to the HREC within 72 hours of the PI becoming aware of the event:

Bellberry Limited HREC
123 Glen Osmond Road Eastwood Adelaide
South Australia 5063
Phone: (08) 8361 3222
Email: bellberry@bellberry.com.au

It is the responsibility of the Sponsor to determine whether a reported SAE fits the classification of a SUSAR. The Investigator's opinion regarding the assessment of expectedness (if provided) and causality will be taken into account in the Sponsor's determination of the SAE as a SUSAR. The causality assessment given by the Investigator cannot be downgraded by the Sponsor.

SUSARs will be reported to regulatory authorities in accordance with national requirements. The Sponsor assumes responsibility for appropriate reporting of SUSARs to the regulatory authorities.

12.6 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant and provide further information to the Sponsor on the participant's condition.

All AEs and SAEs documented at a previous visit/contact that are designated as ongoing, will be reviewed at subsequent visits/contacts. If these have resolved, this should be documented. AEs/SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilises.
- The event returns to Baseline, if a Baseline value is available.
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

The Investigator will ensure that AE/SAE follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the event. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE/SAE. If a participant dies during participation in the study or during a recognised follow-up period, where possible, the Sponsor will be provided with a copy of any post-mortem findings, including histopathology.

12.7 Exposure *In Utero* Management and Reporting

Dosing of the study drug must be discontinued immediately in instances of pregnancies or suspected pregnancies (including a positive pregnancy test regardless of age) in a participant that is on investigational product (including the female partner of a male participant).

The Investigator will notify the Sponsor and designated study safety officer of any pregnancy he/she becomes aware of in female participants or the partners of male participants using an exposure-in-utero form. The pregnant participant (or the male participant's pregnant partner) should be advised to call her healthcare provider.

The Investigator shall obtain informed consent from the pregnant participant (or male participant's pregnant partner) in order to the Investigator (or delegate) to conduct follow-up throughout the gestational period and on the infant following delivery. The Investigator shall follow-up newborn infants that have been exposed to investigational product *in utero* for a minimum of 12 months. Upon discovery of any congenital anomalies (or neonatal deaths) the Investigator shall submit a follow-up report to the Sponsor and Sponsor's designated study safety officer using an SAE form including information regarding the status of the newborn. A miscarriage or any abortion shall also be reported by the Investigator to the Sponsor and Sponsor's designated study safety officer using an SAE form (as per the study SAE Report Form Completion Guidelines).

13 STATISTICS AND DATA ANALYSIS

Detailed methodology for the summation and statistical analysis of the data collected will be documented in a separate Statistical Analysis Plan (SAP) that will be finalised before database lock. Any changes to the methods described in the final SAP will be described and justified as needed in the clinical study report (CSR).

This section describes the general framework to be used for the analysis and presentation of data in this study. The information described in this section may be revised during the study to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution and data that could affect planned analyses.

Generally, summaries will be presented separately for Parts A and B, with summaries presented by treatment group and overall for Part B.

For descriptive statistics, continuous data will be summarised by treatment arm and time point using the number of observations, arithmetic mean, standard deviation (SD), median, minimum and maximum. Discrete data will be summarised using counts and percentages.

All available data will be included in data listings. Data tabulations will be performed for specific analysis populations.

13.1 Sample Size Considerations

The total study sample size was selected to have a high probability of detecting one or more serious adverse events (SAE) if the SAE event rate is 10% or more. If the probability of an SAE is 10%, the probability of observing at least one event in N=35 subjects is over 97%. Looking at Part B only, if the probability of an SAE is 10%, the probability of observing at least one event in N=30 subjects is over 95%.

13.2 Analysis Populations

Full Analysis Set

The Full Analysis Set will include all enrolled participants.

Safety Analysis Set

All participants who receive any study drug will be included in the Safety Analysis Set and will be analysed as per the actual treatment received, if this differs from that to which the participant was randomised.

Pharmacokinetic Analysis Set

The PK Analysis Set will include all participants in the Safety Analysis Set who have at least one study drug concentration determined.

Immunogenicity Analysis Set

The Immunogenicity Analysis Set will include all participants in the Safety Analysis Set who have sufficient data to derive at least one Immunogenicity parameter.

13.3 Disposition

The number of participants enrolled in the study, screen failed participants (if available), participants who completed the study, patients who prematurely withdrew from the study

(including reasons for withdrawal) and the number of patients in each analysis set will be summarized.

13.4 Demographic and Baseline Data

Demographic and baseline data will be presented using the safety analysis set.

Demographic data (including gender, age, race, ethnicity, height, weight, and BMI) will be summarised using descriptive statistics.

Medical history will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The number of participants reported with conditions/procedures and the number of conditions/procedures reported will be summarised, grouped according to system organ class (SOC) and preferred term, using descriptive statistics.

Assessments performed for eligibility only will be listed.

13.5 Prior and Concomitant Medication Data

Prior and concomitant medication data will be presented using the safety analysis set.

Prior and concomitant medications will be coded using the latest version of the World Health Organisation Drug Dictionary (WHO DD). The number and percentage of participants taking prior medication, and concomitant medication will be summarised using frequency tables according to WHO Drug Anatomical Therapeutic Chemical (ATC) Classification Level 1 Code Description and the WHO DD Preferred Name. If a participant has more than one prior or concomitant medication coded to the same preferred name, the participant will be counted only once in the summaries.

13.6 Treatment Compliance and Exposure Data

Treatment compliance and exposure data will be presented using the safety analysis set and full analysis set.

Treatment exposure and compliance will be summarised using descriptive statistics and presented by treatment group and overall.

13.7 Safety and Tolerability Data

All safety analysis will be performed using the safety analysis set.

13.7.1 Adverse Event Data

All AEs will be coded using the latest version of MedDRA by SOC and preferred term, classified from verbatim terms. The number of treatment-emergent AEs (TEAEs) as well as the number and percentage of participants with at least one TEAE, will be summarised by SOC and preferred term. Summaries of TEAEs by severity and relationship will also be presented. Summaries will also be presented for SAEs, TEAEs leading to death or study withdrawal. The duration of all AEs will be determined and included in the listings.

Solicited and unsolicited TEAEs will also be summarised separately. Further details will be provided in the SAP.

13.7.2 Vital Signs

Observed values and changes from baseline for vital signs (systolic and diastolic blood pressure, pulse rate, oral temperature, and respiratory rate) will be summarised at each scheduled timepoint using descriptive statistics.

13.7.3 Nasal Examinations

Nasal examination findings will be listed. Any post-dose clinically significant findings will be reported as AEs.

13.7.4 Physical Examination Data

Physical examination data will be listed only. Any post-dose clinically significant findings will be reported as AEs.

13.7.5 Clinical Laboratory Safety Data

Clinical laboratory safety data will be summarised by laboratory parameter. Observed values and changes from baseline for continuous clinical laboratory parameters will be summarised at each scheduled timepoint using descriptive statistics. Categorical clinical laboratory data will be summarised at each scheduled timepoint using participant counts and percentages. The clinical assessment of laboratory data will be summarised at each scheduled timepoint using participant counts and percentages. Individual participant profiles will be presented for any laboratory parameters with at least one post-dose value outside the laboratory's reference ranges that is deemed clinically significant.

13.7.6 Electrocardiogram

For ECG data, replicate values will be averaged to determine the value of the ECG parameter at each timepoint.

The following ECG parameters will be analysed: PR interval, QRS duration, QTcB, QTcF and ventricular heart rate. Observed values and changes from baseline for ECG parameters will be summarised at each scheduled timepoint using descriptive statistics.

For QTcF, the number of participants with values greater than 450 (and 480, 500) msec or an increase from baseline of at least 30 (and 60) msec will also be tabulated, in accordance with ICH E14 (Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs, CHMP/ICH/2/04).

13.7.7 Nasal Symptoms Sino-Nasal Outcome Test

Scores will be totalled for all 22 symptoms. Changes from baseline in individual total SNOT-22 scores will be calculated as the post-baseline value minus the baseline value. Thus, a negative change will reflect an improvement in the corresponding score. Observed values and changes from baseline will be summarised at each scheduled timepoint by treatment using descriptive statistics and tabulated for each cohort (dose level) and overall.

Individual symptoms will be listed, with the 5 most important issues flagged. The total SNOT score will also be included in the listing.

13.8 Pharmacokinetic Data

All PK analysis will be conducted using PK Analysis Set. Participants with dosing deviations that could potentially affect the PK profile may be excluded from the PK parameter evaluation, at the discretion of the study pharmacokineticist.

Individual participant LMN-301 plasma and nasal mucosal lining fluid concentrations will be listed and summarised using descriptive statistics (n, mean, standard deviation, coefficient of variation [%CV], minimum, maximum, median, geometric mean and geometric coefficient of variation). Individual and mean LMN-301 plasma concentrations over time will be presented graphically with concentration displayed on a linear and a logarithmic scale for each dose group using nominal time points.

Summaries (frequency, means, etc.) will be generated and presented in tabular and/or graphical form.

Due to the sparseness of the PK sampling scheme, no PK parameters will be determined. Serum and nasal drug concentrations be determined at the timepoints presented in Table 21-C and Table 21-D, and will be presented in tabular or graphical form, as appropriate.

If the overall test for group differences is significant, pairwise comparisons between groups will be generated adjusting for multiple comparisons. Additional details will be presented in the SAP.

13.9 Immunogenicity Data

Immunogenicity data will be analysed using the Immunogenicity Analysis Set.

For Part A, serum anti-LMN-301 antibody (possibly binary yes/no, titer, neutralizing) on Day 1 (predose), Day 1 (postdose) and Day 8 will be reported for each subject and presented in tabular or graphical form.

For Part B, serum anti-LMN-301 antibody (possibly binary yes/no, titer, neutralizing) on Day 1 (predose), Day 1 (post dose), Day 3 or 4 (predose), Day 7 (predose) and Day 14 will be reported for each subject and presented in tabular and/or graphical form.

Summaries (frequency, means, etc.) will be generated and presented in tabular and/or graphical form.

If the overall test for group differences is significant, pairwise comparisons between groups will be generated adjusting for multiple comparisons. Additional details will be presented in the SAP.

13.10 Interim Analysis

No interim analyses are currently planned.

14 DATA HANDLING AND RECORD KEEPING

14.1 Privacy of Personal Data

To maintain participant privacy, all eCRFs, study drug accountability records, study reports and communications will identify the participants only by their assigned study number. The PI will grant monitor(s) and auditor(s) designated by the global or local sponsor or regulatory authorities' access to the participant's original medical records for verification of data

recorded in the eCRF and for the purposes of auditing the data collection process. The participant's confidentiality will be maintained at all times and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.2 Screening/Enrolment Logs and Privacy

The PI is required to complete a participant enrolment log to permit reference to each participant during and after the study. Any log identifying study participant identity will be treated as confidential and will be filed by the PI in the Investigator Site File. This document will be reviewed by the study monitor for completeness. To ensure participant confidentiality, if such log is required to be distributed to the Sponsor, it must first have any personal details (e.g., name, initials, date of birth) redacted.

The PI must also complete a screening log, which reports on all participants who were assessed to determine eligibility for inclusion in the study.

14.3 Source Documentation

Source documentation must be prepared and available to capture at a minimum the following aspects and parameters:

- Adherence to protocol procedures
- Participant identification, eligibility, and participation
- Informed consent procedures
- Protocol specified assessments
- Dates of visits
- Safety parameters including reporting and follow-up of AEs and use of concomitant medication
- PK parameters
- Immunogenicity parameters
- Study drug receipt/dispensing/return records
- Study drug administration information
- Date of participant completion
- Discontinuation from treatment, or withdrawal from the study, and the reason if appropriate

Specific items required as source documents will be reviewed with the PI before the study.

The author of an entry in the source documents must be identifiable. Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participants' source documentation.

Following the ICH GCP guidelines, direct access to source documentation and medical records must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data.

14.4 Electronic Case Report Form

An eCRF entry must be completed for each participant who is enrolled and receives at least one dose of study drug. For reasons of confidentiality, the name and initials of the participant should not appear in the eCRF. All eCRF entries, corrections, and alterations must be made by the PI or other authorized study site personnel.

Data entry into the eCRF will be performed throughout study conduct according to the Sponsor's (or delegate) instructions and reviewed by the Sponsor (or delegate) to determine their acceptability. If necessary, eCRF queries will be raised by the Sponsor (or delegate) relating to eCRF data entries. The PI or authorized study site staff must address all eCRF queries raised.

14.5 Recordkeeping and Retention of Records

In compliance with the ICH/GCP guidelines, the PI/institution will maintain all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial. The PI/institution will take measures to prevent accidental or premature destruction of these documents.

Following closure of the study, the PI must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection) and whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems and staff. When permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The PI must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the PI must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The Sponsor will inform the PI of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

If the responsible PI retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

Under no circumstance shall the PI relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the PI must permit access to all study documentation.

The material to be stored shall include, but is not limited to, the following:

- Signed and dated copy of the HREC approved protocol and any HREC approved protocol amendments;
- Signed and dated letter of HREC approval, letter of constitution of the HREC and copies of any other correspondence relevant to the study with the HREC or regulatory authorities;
- The HREC approved original and amended ICFs;
- Current *curriculum vitae* (signed and dated) of the PI and co-workers with major

responsibilities in the trial;
- Site Signature and Delegation of Responsibility Log;
- Financial Disclosure Form(s);
- Blank copy of the study eCRF;
- Signed ICFs;
- Laboratory reference ranges (signed and dated);
- The final clinical study report;

Clinical raw data including the source data forms, all clinical laboratory report forms, participant eCRFs, drug accountability forms, and dispensing records.

15 ETHICS AND REGULATORY COMPLIANCE

15.1 Investigator Responsibilities

The PI must conduct the clinical study in accordance with the HREC approved study protocol, current ICH guidelines for GCP, and applicable regulatory and legal requirements. Good clinical practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

15.2 Regulatory Notification

The requirements for the conduct of clinical trials in accordance with the applicable regulations for each country must be met before commencement of this study.

15.3 Ethical Considerations

This study will be carried out according to the principles of the Declaration of Helsinki, the ICH guidelines for GCP (as adopted in each country/region) and any local guidelines or regulations.

Conduct of the study must be approved by an appropriately constituted HREC before participants are enrolled. Prior to initiation of the study, written HREC approval of the protocol and ICFs, based on the principles of ICH GCP, will be received. This approval will refer to the ICFs and to the study protocol by title and protocol number and will also include date of each document.

A copy of the signed and dated letter of approval will be sent to the study monitor and sponsor prior to study commencement. Any written information and/or advertisements to be used for volunteer recruitment will be approved by the HREC prior to use. A list of the HREC voting members, their titles or occupations, and their institutional affiliations will also be provided to the study monitor and Sponsor before study initiation; or a statement provided that the constitution meets applicable requirements. If approval is suspended or terminated by the HREC, the PI will notify the sponsor immediately.

Protocol amendments that may impact on participant safety or the validity of the study will be approved by HREC, following written agreement for the amendment from the Sponsor. The amended protocol will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

An accurate and complete record of all submissions made to the HREC must be maintained in line with local regulations. The records should be filed in the Investigator Site File and copies must be sent to the Sponsor and maintained in the study Trial Master File.

The Sponsor agrees to abide by the relevant local and/or national guidelines for compensation for injury resulting from participating in a company sponsored research project. Compensation will only be provided on the understanding that the provision of compensation does not amount to an admission of legal liability and is participant to the proposed recipient signing a full and complete release of the company from all claims, damages and costs.

15.4 Informed Consent

Informed consent will be obtained before any volunteer can participate in the study. The ICF will be prepared by the sponsor. The ICF will clearly describe the nature, scope, and potential risks and benefits of the study, in a language that the participant understands. The ICF must also be signed and dated by the person who conducted the informed consent procedure and the participant before the conduct of any study-related activity. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements and adhere to ICH GCP and US FDA guidelines (21 CFR 50) and the requirements in the Declaration of Helsinki. Study participation includes any and all screening and training procedures, as well as any washout of excluded medications.

It is the responsibility of the PI (or the delegate who conducted the informed consent procedure) to obtain a voluntary signed and dated ICF from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of participating in the study. The PI (or delegate) must also explain to the participants that they are completely free to refuse to enter the study or to withdraw from it at any time without prejudice. All eligible participants must receive a full explanation, in layperson's terms, of the aims of the study, the discomfort, risks and potential benefits in taking part as well as of insurance and other procedures for compensation in case of injury. It will be explained that the study is for research purposes only and is not expected to provide any therapeutic benefit to the individual. Each participant will acknowledge receipt of this information by giving written informed consent for participation in the study. All participants will be given a copy of the signed ICF to retain.

Should a protocol amendment become necessary, the ICF may need to be revised to reflect the changes to the protocol. It is the responsibility of the Sponsor (or delegate) to ensure that an amended ICF is reviewed and has received favourable opinion from the HREC, and the PI has to ensure that the amended ICF is signed by all participants subsequently entered in the trial and those currently in the trial, if affected by the amendment.

15.5 Emergency Contact with Principal Investigator

Suitable arrangements must be made for participants to contact the PI or medically trained nominee in the event of an emergency.

15.6 Clinical Laboratory Certification and Reference Ranges

Before the initiation of this study, the PI, or nominee, will obtain a copy of the certification form, with certification number and expiration date for all clinical laboratories used in the study by their site. Reference ranges for each clinical laboratory test used in this study will be obtained from the laboratory that will perform the test during the study.

15.7 Study Completion/Site Closure

The study is considered completed at the last contact of the last participant involved in the study. The final data from the investigational site will be sent to the Sponsor (or designee) in the time frame specified in the Clinical Trial Agreement. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed by the sponsor (or delegate).

15.8 End of Study and Regulatory Notification

At the end of the study, the HREC and relevant regulatory authorities will be notified by the Sponsor (or delegate) according to applicable HREC and regulatory requirements.

16 QUALITY CONTROL AND ASSURANCE

16.1 Study Monitoring

In Australia, the local Sponsor is responsible for assuring the proper conduct of the study regarding protocol adherence and validity of the data recorded in the eCRF. In accordance with applicable regulations and ICH GCP, Avance Clinical will act as the local Sponsor of this study and will be responsible for the assignment of a study monitor who will (on-site or remotely) perform source data verification, monitor drug accountability, ensure that the eCRF is completed correctly and that the protocol is being adhered to.

During the course of the trial, the study monitor will visit the trial site and/or perform remote monitoring at regular intervals. The extent, nature and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrolment rate.

The PI must make themselves available to the Sponsor study monitor during an on-site (or remote) monitoring visit to enable discussion on any arising issues relating to the study.

The PI agrees to allow the study monitor direct access to relevant source documents (original documents, data, and records). Direct access includes permission to examine, analyse, verify, and reproduce any record(s) and report(s) that are important for the evaluation of the clinical trial conduct. The PI also agrees to allocate his/her time and the time of his/her staff to the study monitor to discuss findings and any relevant issues.

Participant confidentiality must be maintained during any monitoring activities conducted by the local sponsor or its delegate(s).

During an on- site (or remote) visit, the study monitor will:

- Check the progress of the study.
- Review study data collected.
- Conduct source data verification.
- Identify any issues and address their resolution.
- Check study treatment accountability records.
- Review biological samples collected for the study and ensure that they are labelled and stored correctly.
- Verify that:
    - The data are authentic, accurate and complete.
    - Safety and rights of participants are being protected.
    - Study is conducted in accordance with the currently approved protocol (and any amendments), ICH GCP and all applicable regulatory requirements.

At study closure, the study monitor will conduct the following activities in conjunction with the PI or site staff as appropriate:

- Ensure that all data queries have been resolved.
- Conduct final accountability and reconciliation for study treatment supplies including inventory and final disposition (e.g., destruction, shipping to repository, etc.).
- Review of site study records for completeness.

16.2 Quality Assurance and Quality Control

To ensure compliance with ICH GCP and all applicable regulatory requirements, the Sponsor (or a designated third party), may conduct a quality assurance audit of the study site. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the PI and Institution agree to notify the Sponsor as soon as possible following awareness of an impending regulatory inspection. The PI and Institution agree to allow the auditor/inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

The Sponsor (or its designee) will perform the quality assurance and quality control activities for this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the sponsor lies with the PI (and delegate(s)) generating the data.

Prior to the study initiation, the sponsor (or its designee) will explain the protocol, IB, and eCRF to the PI and the site staff involved in this study. In addition, the assigned study monitor will be available to explain applicable regulations and to answer any questions regarding the conduct of the study.

16.3 Data Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centres, review of protocol procedures with the PI and associated personnel before the study and conduct of periodic monitoring visits by the sponsor (or designee). Written instructions will be provided for collection, preparation, and shipment of biological samples collected for the purposes of this study. Electronic CRF completion training will be conducted with study personnel before the start of the study. The study monitor will review electronic data for accuracy and completeness during on-site (or remote) monitoring visits and any discrepancies will be resolved with the PI or designee, as appropriate. The data will be entered into the clinical study eCRF and verified for accuracy.

17 FINANCING AND INSURANCE

Financial aspects of the study are addressed in a separate clinical study agreement.

The PI is required to have adequate current insurance to cover claims for negligence and/or malpractice.

The global Sponsor will provide insurance coverage for the clinical study as required by national regulations. The local Sponsor will be subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the study protocol as well as with applicable law and professional standards prior to commencement of the study.

18 PROTOCOL GUIDELINES

18.1 Protocol Deviations

No deviations to the protocol are permitted, except in instances when an emergency occurs that requires a departure from the protocol for an individual. The nature and reasons for the protocol deviation will be recorded in the Clinical Trial Management System and reported at the end of the study in the CSR. Should a non-anticipated protocol deviation occur, the sponsor must be informed as soon as possible.

A minor protocol deviation is an accidental or unintentional change to, or noncompliance with the HREC approved protocol that does not increase risk or decrease benefit; does not have a significant effect on the participant's rights, safety or welfare; and/or on the integrity of the data.

A major protocol deviation is an accidental or unintentional change to, or noncompliance with the HREC approved protocol, which increases risk or decreases benefit, affects the participant's rights, safety, or welfare, or the integrity of the data. Should a major protocol deviation occur, the Sponsor must be informed as soon as possible. Reporting of major protocol deviations to the HREC will be in accordance with applicable regulatory authority mandates.

All deviations, and the reasons for the deviation, will be documented by the PI or designated staff.

18.2 Protocol Waivers

Protocol waivers will not be granted by the Sponsor in this study.

18.3 Protocol Amendments

Protocol revisions of typographical errors, clarifications of confusing wording, and other minor modifications including but not limited to name, address, and contact information changes that have no impact on the safety of the participant, or the science of the study will be classed as **administrative amendments**. Administrative amendments will be submitted to the HREC for information only. The local Sponsor (or designee) will ensure that HREC acknowledgment of administrative changes to the protocol is received and filed.

In all other instances, an amendment to the protocol will be classed as a **substantial amendment** and will be submitted to the HREC for approval and the appropriate regulatory authorities, as applicable. Any substantial amendment to the protocol will be implemented in the conduct of the trial only after approval has been received from HREC.

19 INTELLECUTAL PROPERTY, CONFIDENTIALITY AND PUBLICATIONS

19.1 Ownership

All information provided by the global sponsor and all data and information generated by the clinical facility staff as part of the study (other than a participant's medical records), are the sole property of the study Sponsor.

All rights, title and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by the PI and the clinical facility staff during the course of or as a result of this study are the sole property of the study Sponsor.

Ownership provisions described in this protocol will be superseded by any such provisions included in a legal, written contract between the global sponsor and any stakeholder parties involved in the conduct of this study.

19.2 Confidentiality

All information provided by the sponsor and all data and information generated by the clinical facility as part of this clinical study will be kept confidential by the PI and other site staff. The PI or other site personnel will not use this information and data for any purpose other than conducting the study. These restrictions do not apply to:

- Information which becomes publicly available through no fault of the PI or site staff.
- Information which it is necessary to disclose in confidence to an HREC solely for the evaluation of the study.
- Information which it is necessary to disclose in order to provide appropriate medical care to a study participant, or
- Study results which may be published as described in the Publication Policy (Section 19.3).

Confidentiality provisions described in this protocol will be superseded by any such provisions included in a legal, written contract between the global sponsor and any stakeholder parties involved in the conduct of this study.

19.3 Publication Policy

The Sponsor may publish the results of this study at appropriate times. No publication of the results shall take place without the express consent of the global Sponsor. Publication of the trial results includes but is not limited to conference presentations, scientific conference abstracts or posters, scientific manuscripts, instructional materials or any such public disclosures of the study results generated by the clinical site.

Participant confidentiality shall be maintained and must not be disclosed in any proposed publication materials.

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21 APPENDICES

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21.1 Appendix 1. Schedule of Assessments

21.1.1 Part A (Single Dose)

Table 21-A Schedule of Assessments for Part A Sentinel Cohort (Open-label, single dose)

Please note: the schedule of assessments for Part A appears across 3 pages.

Study Period	Screening	Treatment	Follow-up				EoS
		Week 1			Week 2		
	(-28 to 0)	Day 1	Day 2	Day 3-7	Day 8	Days 9-13	Day 14
Visit Window (days)					±1		±1
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X					
Confinement		X	X				
Outpatient visits	X				X		X
Demographics (age, race, sex, ethnicity)	X						
Medical/Surgical History, Comorbidities	X	X[16]					
Prior and concomitant medications	X	X	X	X	X	X	X
Screening Physical Examination[11]	X						
Targeted Physical Examination[11]		X	X		X		X
Nasal Examination[11]		X					
Height, Weight, BMI	X						
Vital Signs[1]	X	X	X		X		X

Study Period	Screening	Treatment	Follow-up				EoS
		Week 1			Week 2		
	(-28 to 0)	Day 1	Day 2	Day 3-7	Day 8	Days 9-13	Day 14
Visit Window (days)					±1		±1
ECG[10]	X						X
Serum pregnancy test (WOCBP only)	X						
Covid-19 Rapid Antigen Test[12]	X	X					
Urine collection for urinalysis[10]	X						X
Urine pregnancy test (WOCBP only)[13]		X					X
Urine tox screen[2]	X	X					
Alcohol Breath Test	X	X					
FSH (post-menopausal women only)	X						
Viral serology (HIV antibody, HBsAg, HCV)	X						
Clinical Safety Laboratory samples (hematology serum chemistry, coagulation)[10]	X	X	X		X		X
Collect serum for study drug detection[3]		X	X		X		
Collect serum for anti-drug antibodies[4]		X	X		X		
Collect nasal secretion sample[5]		X	X		X		
Administer study drug by intranasal delivery (single dose)		X					
Solicited AEs[6,7]		X	X	X	X	X	X

Study Period	Screening	Treatment	Follow-up				EoS
		Week 1			Week 2		
	(-28 to 0)	Day 1	Day 2	Day 3-7	Day 8	Days 9-13	Day 14
Visit Window (days)					±1		±1
Unsolicited AEs/SAEs[6]		X	X	X	X	X	X
Review diary [15]			X		X		X
Sino-Nasal Outcome Test (SNOT-22)[8]	X	X			X		
Telephone follow-up[9]				X[9]			

Abbreviations: AE=adverse event; BMI=Body mass index; ECG=Electrocardiogram; EoS=End of study; FSH=Follicle stimulating hormone; HBsAg=Hepatitis B surface antigen; HCV=Hepatitis C virus; HIV=Human immunodeficiency virus; RAT=Rapid Antigen Test; SAE=serious adverse event; WOCBP = women of childbearing potential.

1. Vital signs to be measured at pre-dose, and 30 min, 1 hr and 4 hr post-dose on Day 1
2. Urine toxicology screen for drugs of abuse. Urine tox screen and alcohol breath test to be performed at any time predose on Day 1.
3. Serum for detection of study drug will be collected before and 2 hours (±15 mins) after dosing on Day 1, and prior to discharge on Day 2, and during clinic visit on Day 8
4. Serum for anti-drug antibodies will be collected pre-dose and 2 hours (±15 mins) on Day 1, prior to discharge on Day 2 and during clinic visit on Day 8
5. Intranasal mucosal lining fluid (MLF) samples will be collected before and 2 hours (±15 mins) after dosing on Day 1, and once prior to discharge on Day 2, and during clinic visit on Day 8
6. Participants will be provided with a diary to record any solicited and/or unsolicited AEs, and to record concomitant medication usage. Participants will be instructed by site staff on completion during in-person visits
7. Solicited local AEs: stuffy nose, runny nose, sneezing, nasal irritation, nasal tenderness/pain, loss of smell, sore throat scratchy throat, cough
8. Sino-Nasal Outcome Test should be completed at Screening, at 2 hours (±15 mins) post-dose on Day 1, and during clinic visit on Day 8.
9. Research staff to perform daily telephone calls to participants from Days 3-7.
10. Urinalysis and 12-lead ECG to be performed at Screening and at End of Study. Hematology, serum chemistry and coagulation on Day 1 to be performed any time pre-dose.
11. Targeted physical examination to be performed within 1 hour pre-dose. Nasal examination to assess swelling of the mucosa, erythema, and secretions to be performed using nasal speculum and headlight within 1 hour pre-dose and 3 hours post-dose on Day 1.
12. Covid-19 RAT test to be performed at screening and prior to dosing on Day 1. Participants testing positive will not be allowed to participate in the study.
13. Urine pregnancy test to be performed any time prior to dose administration.
14. Clinical Safety Laboratory samples will be collected at 2 hours (±15 mins) pre-dose on Day 1.
15. Site staff to review diary as indicated at each clinic visit. Diary to be collected at the final EoS visit on Day 14.
16. Update only

21.1.2 Part B (Multiple Dose)

Table 21-B Schedule of Assessments for Part B Multi-Dose Cohort (Open-label, multi-dose)

Please note: the schedule of assessments for Part B appears across 4 pages.

Study Period	**Screening**	**Treatment**														**EoS**
	(-28 to 0)	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**	**Day 28**
Visit Window (days)																**±2**
Informed consent	X															
Inclusion/exclusion criteria	X	X														
Outpatient visit: **Group 1**	X	X			X			X			X				X	X
Outpatient visit: **Group 2**	X	X		X		X		X		X		X			X	X
Outpatient visit: **Group 3**	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Demographics (age, race, sex, ethnicity)	X															
Medical/surgical history, comorbidities	X	X[18]														
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Screening Physical Examination	X															
Targeted Physical examination: **Group 1**[12]		X			X			X			X				X	
Targeted Physical examination: **Groups 2 and 3**[12]		X		X				X				X			X	
Nasal Examination: **Group 1**[12]		X			X			X			X				X	
Nasal Examination: **Groups 2 and 3**[12]		X		X				X				X			X	
Height, Weight, BMI	X															

Study Period	**Screening**	**Treatment**														**EoS**
	(-28 to 0)	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**	**Day 28**
Visit Window (days)																**±2**
Serum pregnancy test (WOCBP only)	X															
FSH (post-menopausal women only)	X															
Viral serology (HIV antibody, HBsAg, HCV)	X															
COVID-19 Rapid Antigen Test: Group 1[14]	X	X[14]			X			X			X				X	
COVID-19 Rapid Antigen Test: Groups 2 and 3[14]	X	X[14]		X				X				X			X	
ECG[13]	X															X
Vital Signs: **Group 1**[16]	X	X			X			X			X				X	X
Vital Signs: **Groups 2 and 3**[16]	X	X		X				X				X			X	X
Urine sample for urinalysis[13]	X															X
Urine pregnancy test (WOCBP only) [15]		X														X
Urine drug screen[1]	X	X														
Alcohol breath test	X	X														
Sino-nasal Outcome Test[17]	X	X						X							X	X
Clinical Safety Laboratory blood samples: **Group 1**[16]	X	X			X			X							X	X
Clinical Safety Laboratory blood	X	X		X				X							X	X

Study Period	**Screening**	**Treatment**														**EoS**
	(-28 to 0)	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**	**Day 28**
Visit Window (days)																**±2**
samples: **Groups 2 and 3**[16]																
Collect serum for drug detection: **Group 1**[2]		X			X			X							X	
Collect serum for drug detection: **Groups 2 and 3**[3]		X		X				X							X	
Collect serum for anti-drug antibodies: **Group 1**[2]		X			X			X							X	
Collect serum for anti-drug antibodies: **Groups 2 and 3**[3]		X		X				X							X	
Collect nasal secretion sample: **Group 1**		X[4]			X[5]			X[5]							X	
Collect nasal secretion sample: **Groups 2 and 3**		X[4]		X[5]				X[5]							X	
Administer study drug intranasally: **Group 1**[6]		X			X			X			X					
Administer study drug intranasally: **Group 2**[7]		X		X		X		X		X		X				
Administer study drug intranasally: **Group 3**[8]		X	X	X	X	X	X	X	X	X	X	X	X			
Record solicited and unsolicited AEs/SAEs[9,10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review diary: **Group 1** [19]		X			X			X			X				X	X

Study Period	**Screening**	**Treatment**														**EoS**
	(-28 to 0)	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**	**Day 28**
Visit Window (days)																**±2**
Review diary: **Group 2** [19]		X		X		X		X		X		X			X	X
Review diary: **Group 3** [19]		X	X	X	X	X	X	X	X	X	X	X	X		X	X

Abbreviations: AE=adverse event; BMI=Body mass index; ECG=Electrocardiogram; EoS=End of study; FSH=Follicle stimulating hormone; HBsAg=Hepatitis B surface antigen; HCV=Hepatitis C virus; HIV=Human immunodeficiency virus; IP=Investigational Product; RAT= Rapid Antigen Test; SAE=serious adverse event

1. Urine toxicology screen for drugs of abuse. Urine toxicology screen and alcohol breath test to be done any time pre-dose on Day 1.
2. Serum for detection of study drug and anti-drug antibodies will be collected before and 2 hours (±15 mins) after dosing on Day 1, and prior to dosing on Days 4, 7 and on Day 14 for Group 1 (refer Table 21-D).
3. Serum for detection of study drug and anti-drug antibodies will be collected before and 2 hours (±15 mins) after dosing on Day 1 and prior to dosing on Days 3, 7 and on Day 14 for Groups 2 and 3 (refer Table 21-D).
4. Intranasal mucosal lining fluid sample collected prior to dosing and 2 hours (±15 mins) after dosing on Day 1
5. Intranasal mucosal lining fluid sample collected prior to dosing on Days 3 (Groups 2 and 3), 4 (Group 1), prior to dosing on Day 7 and on Day 14
6. Group 1: Participants in Group 1 will be dosed once every third day during Day 1-12
7. Group 2: Participants in Group 2 will be dosed once **every other day** during Day 1-12
8. Group 3: Participants in Group 3 will be dosed once **every day** during Day 1-12
9. Participants will be provided with a diary to record any solicited and/or unsolicited AEs, and to record concomitant medication usage. AEs to be recorded on each Day 1-28.
10. Solicited local AEs: stuffy nose, runny nose, sneezing, nasal irritation, nasal tenderness/pain, loss of smell, sore throat scratchy throat, cough
11. Vital signs be performed at Day 1 pre-dose, 15 min (± 5 min), 30 min (± 5 min), 1 hr (± 15 min), 4 hr post-dose (± 15 min), and once on Days 3 (Groups 2 &3 only), 4 (Group 1 only), 7, 14 and 28
12. Targeted physical examination to be performed within 1 hour pre-dose on dosing days. Nasal examination to assess swelling of the mucosa, erythema, and secretions to be performed using nasal speculum and headlight within 1 hour pre-dose and 3 hours post dose on Day 1 and then at 3 hours post dose on Day 3 (Groups 2 and 3 only) or Day 4 (Group 1), 3 hours post dose on Day 7, 3 hours post dose on Day 10 (Group 1) or Day 11 (Group 2 and 3) and on Day 14.
13. Urinalysis and ECG to be performed at Screening and at End of Study
14. Covid-19 RAT test to be performed at screening and prior to dosing on Day 1 Day 3 (Groups 2 and 3 only) or Day 4 (Group 1), Day 7, Day 10 (Group 1) or Day 11 (Group 2 and 3) and Day 14. Participants testing positive will not be permitted to participate in the study.
15. Urine pregnancy test to be performed any time prior to dose administration on Day 1; otherwise, may be performed any time on the scheduled day.
16. To be performed within 1 hour prior to dose administration on dosing days; otherwise, may be performed any time on the scheduled day.
17. Sino-Nasal Outcome Test to be performed at 2 hours (±15 mins) post-dose on dosing days; otherwise, test may be performed at any time on the scheduled day.
18. Update only.
19. Site staff to review diary at each clinic visit. Diary to be collected at the final EoS visit on Day 28.

21.2 Appendix 2. Pharmacokinetic and Immunogenicity Sampling Schedule

Note: Where required, the timing of post-dose procedures will be in reference to administration of the last actuation completed

21.2.1 Part A (Single Dose)

Table 21-C Pharmacokinetic and Immunogenicity Sampling Schedule (Part A, Single Dose)

Day	Timepoint	PK (blood)	PK (nasal secretions)	Immunogenicity (plasma)	Time Window
1	Pre-dose	X	X	X	Any time prior to dose administration on the day
	Dose				
	2 hr post-dose	X	X	X	± 15 min
2	Any	X	X	X	Any time on day
8	Any	X	X	X	Any time on day

Abbreviations: PK = pharmacokinetic.

21.2.2 Part B (Multiple Dose)

Table 21-D Pharmacokinetic and Immunogenicity Sampling Schedule (Part B Multiple Dose)

Day	Timepoint	PK (blood)	PK (nasal secretions)	Immunogenicity (plasma)	Time Window
1	Pre-dose	X	X	X	Any time prior to dose administration on the day
	First Dose				
	2 hr post-dose	X	X	X	± 15 min
3 (Groups 2 & 3 only)	Pre-dose	X	X	X	Any time prior to dose administration on the day
4 (Group 1 only)	Pre-dose	X	X	X	Any time prior to dose administration on the day
7	Pre-dose	X	X	X	Any time prior to dose administration on the day
14	End of Study	X	X	X	Any time on the day of EoS visit

Abbreviations: PK = pharmacokinetic.

21.3 Appendix 3 Vital Signs Assessment Schedule

Note: Where required, the timing of post-dose procedures will be in reference to administration of the last actuation completed

21.3.1 Part A (Single Dose)

Table 21-E Vital Signs Assessment Schedule (Part A, Single Dose)

Day	Timepoint	Vital Signs[1]	Time Window
Screen	-	X	Any time on the scheduled day
1	pre-dose	X	Within 2 hour prior to dose administration
	Dose		
	30 min post-dose	X	± 5 min
	1 hr post-dose	X	± 15 min
	4 hr post-dose	X	± 15 min
2	24 hr post-dose	X	± 2 hrs
8	-	X	Any time on the scheduled day

[1] Includes pulse rate, blood pressure, oral temperature and respiratory rate

21.3.2 Part B (Multiple Dose)

Table 21-F Vital Signs Assessment Schedule (Part B, Multiple Dose)

Day	Timepoint	Vital Signs[1]	Time Window
Screen	-	X	Any time on the scheduled day
1	1 hr pre-dose	X	Within 1 hour prior to dose administration
	Dose		
	15 min post-dose	X	± 5 min
	30 min post-dose	X	± 5 min
	1 hr post-dose	X	± 15 min
	4 hr post-dose	X	± 15 min
3 (Groups 2 & 3 only)	-	X	Any time on the scheduled day
4 (Group 1 only)	-	X	Any time on the scheduled day
7	-	X	Any time on the scheduled day
14	-	X	Any time on the scheduled day
28	-	X	Any time on the scheduled day

[1] Includes pulse rate, blood pressure, oral temperature and respiratory rate

21.4 Appendix 4. Highly Effective Forms of Birth Control

A highly effective method of contraception is one that has a failure rate of < 1% when used consistently and correctly and for this clinical study include the following:

For female participants (of childbearing potential):

- Established use of oral, injected or implanted hormonal methods of contraception for at least 1 month prior to Screening (SV1 for Phase Ib, MAD).
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Vasectomised partner (i.e., a female participant's male partner has undergone effective surgical sterilisation (i.e., documented azoospermia at least 90 days after the procedure) before the female participant entered the clinical trial and he is the sole sexual partner of the female participant during the clinical trial)
- Abstinence from heterosexual intercourse (acceptable only if it is the participant's usual form of birth control/lifestyle choice)
- Bilateral tubal occlusion

Examples of non-acceptable methods of contraception include:

- Condoms alone or double barrier
- Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation)
- Withdrawal

For female partners (who are of childbearing potential) of male participants:

- Established use of oral, injected or implanted hormonal methods of contraception for at least 1 month prior to Screening (SV1 for Phase Ib, MAD).
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Vasectomised partner (i.e., the male participant has undergone effective surgical sterilisation before entering the clinical trial)
- Bilateral tubal occlusion

Note that female participants who have been surgically sterilised (hysterectomy, bilateral salpingectomy, bilateral oophorectomy at least 6 weeks before the screening visit) or postmenopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause and a follicle-stimulating hormone (FSH) level consistent with postmenopausal status, per local laboratory guidelines), are not considered to be of childbearing potential.

21.5 Appendix 5: Clinical Laboratory Assessments

<table>
<tr><th colspan="3">Safety Assessments</th></tr>
<tr><th>Haematology</th><th>Serum Chemistry, Including Liver Function</th><th>Coagulation</th></tr>
<tr><td rowspan="2">• Haemoglobin
• Haematocrit
• Mean cell hemoglobin (MCH)
• Mean cell volume (MCV)
• Mean corpuscular hemoglobin concentration (MCHC)
• Platelet count
• RBC count
• Red cell distribution width
• Reticulocyte count
• WBC count
• Differential and leukocyte count (basophils, eosinophils, lymphocytes, monocytes, neutrophils)</td><td rowspan="2">• Albumin
• Alkaline phosphatase
• ALT
• Anion gap
• ASTBicarbonate
• Urea
• Calcium
• Calcium (adjusted)
• Chloride
• Creatinine
• eGFR
• GGT
• Globulin
• Ionised calcium
• Lactate dehydrogenase
• Phosphorus
• Potassium
• Sodium
• Total bilirubin
• Direct bilirubin
• Indirect bilirubin
• Total protein
• Urea
• Uric acid
• Creatinine</td><td>• PT
• APTT
• INR</td></tr>
<tr><td>Urinalysis [1]
• Bilirubin
• Blood
• Glucose
• Ketones
• Leukocyte esterase
• Nitrites
• pH
• Protein
• Specific gravity
• Urobilinogen

[1] Urine sediment microscopy will be conducted in the instance of abnormal urinalysis findings for blood and leukocyte esterase.</td></tr>
<tr><th colspan="3">Other Assessments</th></tr>
<tr><th>Pregnancy Test</th><th>Follicle-Stimulating Hormone</th><th>Viral Serology</th></tr>
<tr><td>• Urine hCG
• Serum hCG [2]

[2] If the urine hCG is positive, pregnancy will be confirmed by a serum hCG test</td><td>FSH</td><td>HIV antibody
HBsAg
HCV antibody</td></tr>
<tr><td>Urine Drugs of Abuse
Amphetamines
Methamphetamines
Methadone
Barbiturates
Benzodiazepine
Cocaine
Opiates
Phencyclidine
Tetrahydrocannabinol</td><td colspan="2"></td></tr>
<tr><td colspan="3">Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; FSH = follicle-stimulating hormone; HBsAg = Hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = Human Immunodeficiency Virus; RBC = red blood cell; ULN = upper limits of normal; WBC = white blood cell.</td></tr>
</table>