STATISTICAL ANALYSIS PLAN

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STATISTICAL ANALYSIS PLAN

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

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List of Abbreviations

Abbreviation	Description
ADA	Anti-drug Antibody
ADR	Adverse Drug Reaction
AEs	Adverse Events
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
BLQ	Below The Limit of Quantifiable
CS	Clinically Significant
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRFs	Electronic Case Report Forms
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
ID	Identification
IGS	Immunogenicity Analysis Set
IN	Intranasal
INR	International Normalized Ratio
MedDRA	Medical Dictionary for Regulatory Activities
MLF	Mucosal Lining Fluid
NCS	Not Clinically Significant
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
PT	Preferred Terms
PT	Prothrombin Time
SAEs	Serious Adverse Events
SAM	Synthetic Absorptive Matrix
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SNOT-22	Sino-Nasal Outcome Test
SOC	System Organ Class
SOPs	Standard Operating Procedures
SS	Safety Analysis Set
TEAEs	Treatment Emergent Adverse Events
TFLs	Tables, Listings, And Figures
UDS	Unidose

UN	Unknown
UNK	Unknown
WBC	White Blood Cells
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data collected for Lumen Bioscience, Inc protocol titled: "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" dated 25 May 2023 (Version 1.0).

The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock, reasons for such deviations, and all alternatives or additional statistical analyses that may be performed will be described the Clinical Study Report (CSR).

2 PROJECT OVERVIEW

2.1 Description of 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 intranasally (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-specific 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 text (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 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.

2.2 Objectives

2.2.1 Primary Objectives and Endpoints

The primary objective of this study is:

- To determine the safety and tolerability of single and multiple doses of intranasally delivered LMN-301.

The primary endpoints of this study are:

- 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 (SNOT-22).

2.2.2 Secondary Objectives and Endpoints

The secondary objective of this study is:

- To determine the persistence profile of LMN-301 in the nasal mucosa following single and multiple doses.

The secondary endpoints of this study are:

- Detect the presence of LMN-301 in nasal mucosal lining fluid samples collected from study participants.

2.2.3 Exploratory Objectives and Endpoints

The exploratory objective of this study is:

- To detect the presence of LMN-301 and anti-drug antibodies in serum.

The primary endpoints of this study are:

- Detection of LMN-301 virus-binding proteins and, if virus-binding proteins are detected, anti-virus binding protein IgG in serum samples.

3 SAMPLE SIZE

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%.

4 STATISTICAL CONSIDERATIONS

4.1 Standard Operating Procedures and Software

Data will be handled and processed per the sponsor representative's (Avance) Standard Operating Procedures (SOPs), which are written based on the principles of Good Clinical Practice (GCP).

All data conversions and statistical analyses will be performed using SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA) with program code prepared specifically for the study by qualified Avance statisticians and SAS® programmers.

4.2 General Considerations

All data collected during the study (data originating from the electronic Case Report Forms (eCRFs) or electronic transfers will be presented in the data listings. Event-based listings will be sorted by treatment group, participant identifier and event start date/time (i.e., AE start date/time). Assessment-based listings will be sorted by treatment group, parameter name (alphabetically unless specifically stated otherwise), participant identifier, visit and time point (if applicable).

Unless otherwise stated, the following methods will be applied:

- Continuous variables: Descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation, median, minimum and maximum values.

  The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean and median values will be displayed to one more decimal than the source data, and the SD values will be displayed to two more decimals than the source data for the specific variable.

  The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the abovementioned rules.

- Categorical variables: Descriptive statistics will include frequencies and percentages per category. The denominator in all percentage calculations will be the number of participants in the relevant analysis population with non-missing data, unless specifically stated otherwise. Percentages will be rounded to one decimal place and will not be displayed for zero frequencies.

- Presentation of p-values and confidence intervals: 95% confidence intervals will be computed, and reported to four significant figures, p-values will be displayed up to three decimal places and as "<0.001" if the value is below 0.001.

- Repeat/unscheduled assessments: Only values collected at scheduled study visits/time points will be presented in summary tables. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point. All collected data will be included in the data listings. If an unscheduled visit was intended to replace the missing assessment for a scheduled visit this should be documented clearly before values are carried forward as a scheduled visit assessment.

- Assessment windows: All assessments will be included in the data listings and the protocol specified visit windows will not be applied to exclude assessments that were not performed on the protocol specified visit days. Protocol visit windows will be as per CRF data collection.
- Result display convention: Results will be centre aligned in all summary tables and listings. Participant numbers, visit, and parameter labels and comments may be left aligned if required.
- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:
    - Date only: DD-MMM-YYYY
    - Date and time: DD-MMM-YYYY/HH:MM

  If only partial information is available, unknown components of the date or time will be presented as UN (Unknown), for example "UN-UNK-2020" or "UN:UN" for time.

4.3 Key Definitions

The following definitions will be used:

- Date of the First Study Treatment Administration: The date of the first study treatment administration is defined as the earliest date on which a study treatment was administered.
- Date of the Last Study Treatment Administration: The date of the last study treatment administration is defined as the latest known date on which a study treatment was administered.
- Baseline: The Baseline value is defined as the last available valid, non-missing observation (including repeat and unscheduled assessments) for each Participant prior to first study treatment administration on Day 1.

  For ECG triplicates, the baseline is defined as the mean of the last set of triplicates performed prior to first study treatment administration.

  For SNOT-22 results, the baseline is defined as the total score (as defined in section XX) of the last SNOT-22 test performed prior to first study treatment administration.
- Change from Baseline: The change from Baseline value is defined as the difference between the result collected/derived at a particular visit and the Baseline value.

  The change from Baseline value at each visit will be calculated for all continuous parameters using the following formula:

  Change from Baseline Value = Result at specified visit – Baseline Value

  The change from Baseline value will only be calculated if the specific visit result and the Baseline value for the parameter are both available and will be treated as missing otherwise.

- Study Day: The study day of an event is defined as the relative day of the event starting with the date of the first study treatment administration (reference date) as Day 1 (there will be no Day 0).

The study day of events occurring before the first study treatment administration will be calculated as:

Study Day = (Date of Event - Date of First Study Treatment Administration)

For events occurring on or after Day 1, study day will be calculated as:

Study Day = (Date of Event - Date of First Study Treatment Administration) + 1

Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the end of the study.

- Actual Time from First Dose (hours) in PK related outputs is defined as:

  (Date/Time of PK Sample collection) – (Date/Start Time of First Dose on Day 1).

- Actual Time Deviation (hours) in PK related outputs is defined as:

  (Actual PK Sample Collection Time Post Dose) – (Scheduled PK Sample Collection Time Post Dose).

- AE Duration: Adverse event duration (in days, to two decimal places), calculated as

  (Resolution Date + Resolution Time) – (Onset Date + Onset Time)

  AE duration will only be calculated for events with complete dates/times and will be undefined for events that are 'Ongoing' at the end of the study.

- Any quantitative laboratory parameters that are given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (e.g., <2.2 will be imputed as 2.2) for the calculation of the changes from baseline and for the descriptive statistics. In the listings, no imputations will be performed, and all data will be displayed as recorded in the database.

- Laboratory Parameters:

  The L/N/H indicator will be derived, where both the lower and upper limit of the reference range was provided, by following derivation:
  - If the result is less than the lower limit of the reference range, the indicator will be set as "Low".
  - If the result is greater than the upper limit of the reference range, the indicator will be set as "High".
  - If the result is greater or equal to the lower limit of the reference range and less or equal to the upper limit of the reference range, the indicator will be set as "Normal".

4.4 Multiple Comparisons and Multiplicity

A Bonferroni correction will be explored for Immunogenicity model analysis (Section 15). Both adjusted and unadjusted p-values will be presented.

4.5 Handling of Missing Data

In general, all data will be analysed as collected and missing values will not be imputed or replaced unless stated otherwise.

4.6 Treatment Group and Visit Display Conventions

Summary Tables:

In summary tables, the representation as below:

Part A:

- Sentinels *(50mg once only)*

Part B:

- Group 1 *(50mg every 3rd day)*
- Group 2 *(50mg every 2nd day)*
- Group 3 *(50mg daily)*
- Overall *(Part B subjects)*

Data Listings:

In data listings, the following labels will be used:

Part A:

- Sentinels

Part B:

- Group 1
- Group 2
- Group 3

Visit labels:

The following visit labels will be used:

- Screening (Listing only)
- Day 1 (Listing only)
- Baseline (Table only)
- 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
- Early Termination (Listing only)
- Unscheduled (Listing only)

For listings, the visit representing baseline (either screening or unscheduled visit) will be marked as "[1]" with a footnote indicating it is baseline value. These visit displays will be sorted by date of visit within each participant.

5 ANALYSIS POPULATIONS

5.1 Full Analysis Set (FAS)

The Full Analysis Set will include all enrolled participants.

5.2 Safety Analysis Set (SS)

The Safety Analysis Set will include all participants who receive study drug and will be analyzed as per the treatment group they were assigned to.

5.3 Pharmacokinetic Analysis Set (PKS)

The Pharmacokinetic Analysis Set will include all participants in the Safety Analysis Set who have at least one study drug concentration determined. Pharmacokinetic analysis will be conducted outside of Avance and will be detailed in a separate Pharmacokinetic Analysis Plan.

5.4 Immunogenicity Analysis Set (IGS)

The Immunogenicity Analysis Set will include all participants in the Safety Analysis Set who have sufficient data to derive at least one immunogenicity parameter. Immunogenicity analysis will be conducted outside of Avance and will be detailed in a separate Immunogenicity Analysis Plan.

6 PARTICIPANT ENROLMENT AND DISPOSITION

The following participant enrolment and disposition information will be reported:

Summary of Enrolment:

- Number of Screen Failures
- Reason for Screen Failure (percentage denominator based on number of screen failures)
- Number of Participants Treated (to receive at least one dose of study drug)

Summary of Disposition:

- Number of Participants Completed
- Number of Participants Not Completed
- Reason for Non-Completion (percentage denominator based on number of withdrawn participants)

Counts and percentages will be reported for summary of enrolment and disposition and will be provided using the FAS population for treatment groups defined in section 4.6.

Listings will be provided for summary of enrolment along with the date the participant provided informed consent/reconsent, eligibility, date of randomisation/randomisation number, reason for screen failure, date received study drug and sorted by participant ID for FAS population.

Listings will be provided for summary of disposition along with the date the participant provided informed consent/reconsent, the date of study completion/discontinuation and the primary reason for non-completion. The listing will be provided by treatment groups defined in section 4.6 sorted by participant ID for the FAS population.

7 ANALYSIS SET

The following analysis set information will be reported:

- Participants included in the Full Analysis Set
- Participants included in Safety Analysis Set

Counts and percentages for these participants under different population sets will be provided using the FAS population for treatment groups defined in section 4.6.

Listings will be provided by treatment groups defined in section 4.6 sorted by participant ID for the FAS population.

8 PROTOCOL DEVIATIONS

Prior to database lock, all protocol deviations will be reviewed between Avance medical monitors and the Sponsor.

The number of participants with at least one protocol deviation, those with at least one major protocol deviation, and the category and grading of protocol deviations will be summarized in accordance with section 4.2 using the SS population for treatment groups defined in section 4.6, in addition to the number of occurrences of each protocol deviation.

Listing of all protocol deviations will be provided by treatment groups defined Section 4.6 sorted by participant ID for the SS population.

9 DEMOGRAPHICS

The demographics variables to be reported are listed below:

- Age (years)
- Sex
- Women of child-bearing potential
- Race
- Ethnicity
- Height (cm) at screening
- Weight (kg) at screening
- BMI (kg/m^2) at screening

These variables will be summarized using descriptive statistics in accordance with section 4.2 under the SS population for treatment groups defined in Section 4.6. Demographics variables will also be listed by treatment groups defined in section 4.6 under the SS population sorted by participant ID.

9.1 Pregnancy and Follicle Stimulating Hormone (FSH) Test

All available pregnancy test and FSH results will be displayed in a data listing by treatment groups defined in section 4.6, sorted by participant ID for the SS population, along with age, sex, race and baseline weight of the participant.

9.2 Alcohol Breath Test

All available alcohol breath test results will be displayed in a data listing by treatment groups defined in section 4.6, sorted by participant ID for the SS population, along with age, sex, race and baseline weight of the participant.

9.3 Urine Drug Screen

All available urine drug screen results will be displayed in a data listing by treatment groups defined in section 4.6, sorted by participant ID for the SS population, along with age, sex, race and baseline weight of the participant.

9.4 Serology Assessment

All available serology results (including HIV-1, HIV-2, HBsAg, HCV antibody) will be displayed in a data listing by treatment groups defined in section 4.6, sorted by participant ID for the SS population, along with age, sex, race and baseline weight of the participant

9.5 COVID-19 Assessment

All available COVID-19 rapid antigen test (RAT) results will be displayed in a data listing by treatment groups defined in section 4.6, sorted by participant ID for the SS population, along with age, sex, race and baseline weight of the participant.

10 MEDICAL HISTORY

Medical history conditions will be coded using the latest versionof the Medical Dictionary for Regulatory Activities (MedDRA) that is available at the time of study commencement. The version used for coding will be specified in the footnote of the relevant outputs.

Terms will be coded to the full MedDRA hierarchy, but the system organ class (SOC) and preferred terms (PT) will be of primary interest for the analysis.

Participants with any medical history (MedDRA SOC and PT) will be summarized using counts (events and participants) and percentages for the SS population by treatment groups defined in section 4.6. Where SOC and PT are reported, the display will be sorted by descending order of occurrences of SOC and PT, followed by alphabetical sorting. In Part B, summaries will be sorted based on counts in the overall treatment group.

Medical history listings will be provided by treatment groups as defined in section 4.6, sorted by participant ID for the SS population, along with start date, end date, and ongoing status of medical history.

11 PRIOR AND CONCOMITANT MEDICATION

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD) (the version of WHODRUG GLOBAL B3 September 2022).

- Prior Medications: Prior medications are defined as any medication where the use was stopped prior to the first administration of the study medication.
- Concomitant Medications: Concomitant medications are defined as medications (other than the study drug) taken at least once after the start of first study drug administration.

  If a clear determination cannot be made as to whether the medication is concomitant or not due to missing or incomplete data, the medication will be treated as concomitant medication taken during the study.

The number and percentage of participants using at least one concomitant medication will be displayed together with the number and percentage of participants using at least one medication within each anatomical therapeutic class (ATC-Level 1) and preferred name. These will be summarized under the SS population for treatment groups defined in section 4.6 and repeated for prior medication. Where ATC-Level 1 and preferred name are reported, the display will be sorted by descending order of occurrences of ATC-Level 1 and PT, followed by alphabetical sorting. In Part B, summaries will be sorted based on counts in the overall treatment group.

Listing of full details of prior and concomitant medications (medication taken, therapeutic class, start and stop dates/ongoing status, indication, routes, frequency, and dosage) will be provided by treatment groups defined in section 4.6, sorted by participant ID and start date for the SS population.

For concomitant therapeutic procedures, procedure terms will be coded using version 25.1 of the Medical Dictionary for Regulatory Activities (MedDRA). Listing of full details of concomitant procedures (procedure, SOC, PT, start dates and indication) will be provided by treatment groups defined in section 4.6, sorted by participant ID and start date for the SS population.

The number and percentage of participants having at least one concomitant procedure will be displayed together with the number and percentage of participants having at least one procedure within each system organ class (SOC) and procedure parent term (PT). These will be summarized under the SS population for treatment groups defined in section 4.6. Where SOC and PT are reported, the display will be sorted by the descending order of occurrences of SOC and PT, followed by alphabetical sorting. In Part B, summaries will be sorted based on counts in the overall treatment group.

12 TREATMENT COMPLIANCE AND EXPOSURE

All study drug administration information (study drug administered [Yes/No], study day, reason not administered, fasting status, reason for not fasting, date and time of administration, dose [mg]) will be listed by treatment groups defined in section 4.6, sorted by participant ID and study day for the SS population.

Treatment Compliance during the treatment period is defined as:

$$\frac{\text{Total number of doses administered}}{\text{Expected number of doses based on the treatment regimen received}} * 100\%$$

The total number of tablets administered for each treatment is defined as:

- Part A:
    - Sentinels: 1 dose
- Part B:
    - Group 1: 4 doses
    - Group 2: 6 doses
    - Group 3: 12 doses

Treatment Exposure during the treatment period is defined as:

$$\text{Date of last dose of study drug} - \text{Date of first dose of study drug} + 1$$

Treatment compliance and exposure rates will be summarised using descriptive statistics by treatment groups defined in section 4.6 for the SS population. Treatment compliance and exposure rates will also be listed by treatment groups defined in section 4.6, sorted by participant ID for the SS population.

13 SAFETY

All safety endpoints will be analyzed using the SS population.

13.1 Adverse Events

AE verbatim terms will be coded using the version 25.1 of the Medical Dictionary for Regulatory Activities (MedDRA). AEs and SAEs are defined in the study protocol.

- Treatment Emergent Adverse Events (TEAEs) are defined as adverse events that occurred or worsened from the first administration of study drug. If determination cannot be made as to whether the event is treatment emergent due to missing or incomplete data, the adverse event will be treated as treatment emergent.
- Treatment-Related AEs are defined as any TEAEs reported with the causality of "Related" to study treatment.
- Solicited AEs will be assessed by direct questioning and include stuffy nose, runny nose, sneezing, nasal irritation, nasal tenderness/pain, loss of smell, sore/scratchy throat, and cough.
- Unsolicited AEs include all other AEs not classified as Solicited adverse events.

All AE summaries will be restricted to TEAEs only.

The TEAE summaries will include:

- Overall Summary of TEAEs
    - TEAEs
    - TEAEs by Severity (Grade 1 to Grade 5)
    - TEAEs by Relationship
    - Treatment Related TEAEs
    - Serious TEAEs
    - Treatment Related Serious TEAEs
    - Solicited TEAEs
    - Unsolicited TEAEs
    - TEAEs leading to Death
    - TEAEs leading to Study Withdrawal

The following table summaries will be presented by SOC and PT by treatment groups defined in Section 4.6:

- TEAE summary by SOC and PT
- TEAE summary by SOC, PT and Severity
- TEAE summary by SOC, PT and Relationship
- Treatment Related TEAE summary by SOC and PT
- Treatment Related TEAE summary by SOC, PT and Severity

- Serious TEAE summary by SOC and PT
- Treatment Related Serious TEAEs summary by SOC and PT
- Solicited TEAE summary by SOC and PT
- Unsolicited TEAE summary by SOC and PT

The above items will be presented using summary tables, which will include the number of participants (%) experiencing an event and the number of events. If a participant experienced the same adverse event multiple times, this will only be counted once for the purpose of counting the number of participants experiencing that adverse event. Summary tables will be done for the SS population for treatment groups defined in Section 4.6. Where SOC and PT are reported, the display will be sorted by the descending order of occurrences of SOC and PT, followed by alphabetical sorting. In Part B, summaries will be sorted based on counts in the overall treatment group.

All AEs will be listed and will include the verbatim term, SOC, PT, SAE, start/end date/time, causality/severity, relationship to study treatment, outcome, action taken, solicited [yes/no] and study withdrawal. A separate listing will be created for SAEs, those leading to Death, and those leading to Study Withdrawal. These listings will be presented by treatment groups defined in section 4.6, sorted by participant ID and AE start date for the SS population, along with age, sex, race, and baseline weight of the participant.

13.2 Safety Laboratory Assessments

The following laboratory measurements will be taken at the time points specified in the study procedure schedule:

- Haematology: Haemoglobin, haematocrit, mean cell haemoglobin (MCH), mean cell volume (MCV), mean corpuscular haemoglobin concentration (MCHC), platelet count, red blood cell count, red cell distribution width, reticulocyte count, white blood cell count with differentials (leukocytes, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
- Chemistry: Albumin, alkaline phosphatase, alanine aminotransferase (ALT), anion gap, aspartate aminotransferase (AST), bicarbonate, urea, calcium (+ adjusted), chloride, creatinine, estimated glomerular filtration rate (eGFR), gamma-glutamyl transferase (GGT), globulin, ionised calcium, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, indirect bilirubin, total protein, urea, uric acid
- Coagulation: Activated Partial Thromboplastin Time (aPTT), International Normalised Ratio (INR), Prothrombin Time (PT)
- Urinalysis and Urine Microscopy: Bilirubin, blood, glucose, ketones, leukocyte esterase, nitrites, pH, protein, specific gravity, urobilinogen

For the haematology, chemistry, and coagulation, continuous data summary statistics (as described in Section 4.2) will be presented for values and change from baseline value at baseline and each scheduled post baseline visit.

In addition, shift tables from baseline at each visit for haematology, chemistry, and coagulation lab parameters (low, normal, and high) will also be presented using counts and percentages.

For urinalysis, discrete data summary statistics (as described in Section 4.2) will be presented for the counts and percentages of normal, abnormal clinically significant (CS) and non-clinically significant (NCS) at each visit results at baseline and each schedule post baseline visit.

These summary tables will be based on the SS population for treatment groups defined in Section 4.6.

The listings of laboratory parameters (haematology, chemistry, coagulation, and urinalysis) will include all the information collected. In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values (where applicable) at each scheduled post baseline (scheduled and unscheduled) visit will be presented. In addition, a separate listing will be generated for any individual laboratory results assessed as clinically significant.

These listings will be presented by treatment groups defined in section 4.6, sorted by participant ID and visit for the SS population, along with age, sex, race, and baseline weight of the participant.

13.3 Vital Sign Assessments

The following vital signs measurements will be taken at the time points specified in the study procedure schedule:

- Systolic blood pressure (SBP) (mmHg) [Reference range: 90-160 mmHg]
- Diastolic blood pressure (DBP) (mmHg) [Reference range: 50-95 mmHg]
- Pulse Rate (beats/min) [Reference range: 45-100 beats/min]
- Temperature (ºC) [Reference range: 35.5-27.7 ºC]
- Respiratory Rate (breaths/min) [Reference range: 12-22 breaths/min]
- Overall Clinical Interpretation:
    - Normal
    - Abnormal NCS (Not Clinically Significant)
    - Abnormal CS (Clinically Significant)

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, ‘Systolic Blood Pressure (mmHg)’. Parameters will be sorted in the order that the measurements were collected in on the Vital Signs eCRF page within the tables and listings.

Summary statistics for vital sign parameters in accordance to section 4.2 will be presented for baseline and for each scheduled post baseline visit (which also includes change from baseline). In addition, overall clinical interpretation result (Normal, Abnormal Not Clinically Significant (NCS), Abnormal Clinically Significant (CS)) will be summarized by counts and percentages for baseline and each scheduled post baseline visit. These summary tables will be generated using the SS population for treatment groups defined in Section 4.6.

In addition, shift tables from baseline at each visit for vital sign parameters (normal, low and high) will also be presented using counts and percentages.

The listing of vital sign parameters will include all the information collected. In addition, the observations that are used as the baseline record for each parameter will be flagged, and the change from baseline values at each post baseline (scheduled and unscheduled) visit will be presented. This listing will be presented by treatment groups defined in section 4.6, sorted by participant ID and visit for the SS population, along with age, sex, race, and baseline weight of the participant.

13.4 Electrocardiogram (ECG)

The following ECG measurements will be taken at the time points specified in the study procedure schedule (section 20):

- Heart Rate (bpm) [Reference range: 45-100 bpm]
- PR interval (msec) [Reference range: 120-220 msec]
- QRS duration (msec) [Reference range: <120 msec]
- QTcB & QTcF internal (msec) [Reference range: ≤470 msec (females), ≤450 msec (males)]
- Overall Investigator Finding
    - Normal
    - Abnormal NCS
    - Abnormal CS

The mean/average of ECG triplicates at applicable visit/timepoints for each participant will be derived and displayed in the data listing along with the original triplicates. For ECG interpretation, the worst ECG triplicate will be used and displayed in the mean of ECG triplicate.

In summary tables, the mean of ECG triplicates will be used, and the baseline of ECG triplicates will be as defined in section 4.3.

Summary statistics for ECG parameters in accordance with section 4.2 will be presented for baseline and for each scheduled post baseline visit (which also includes the change from baseline). In addition, clinical result of ECG interpretation (Normal, Abnormal NCS, and Abnormal CS) will be summarized by counts and percentages for baseline and for each scheduled at post baseline visit. These summary tables will be generated using the SS population for treatment groups defined in section 4.6.

The listing of ECG parameters will include all the information collected. In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values at each post baseline (scheduled and unscheduled) visit will be presented. This listing will be presented by treatment groups defined in section 4.6, sorted by participant ID and visit for the SS population, along with the age, sex, race and baseline weight of the participant.

13.5 Physical Examination

The listing of complete and targeted physical examinations will include all the information collected. This listing will be presented by treatment groups defined in section 4.6, sorted by participant ID and visit for the SS population.

13.6 Nasal Examination

The listing of macroscopic nasal examinations will include all the information collected. This listing will be presented by treatment groups defined in section 4.6, sorted by participant ID and visit for the SS population.

13.7 Nasal Symptoms Sino-Nasal Outcome Test (SNOT-22)

A SNOT-22 questionnaire will be given at the time points specified in the study procedure schedule. The SNOT-22 consists of twenty-two questions assessing the participant's experience with each of the listed symptoms on a scale of 0-5, based on symptoms over the preceding two weeks. The rating scale is 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 five of the most important issues affecting them from the list of twenty-two symptoms.

The 22 questions will be totalled and values (including change from baseline) summarized using descriptive statistics in accordance with section 4.2 under the SS population for treatment groups defined in Section 4.6. A negative change will reflect an improvement in the corresponding score.

The listings of SNOT-22 responses will include all the individual symptoms information, with the 5 most important issues flagged. In addition, the total score will be displayed with the observations used as the baseline record (value) flagged, and the change from baseline values (where applicable) at each scheduled post baseline (scheduled and unscheduled) visit presented.

These listings will be presented by the treatment groups defined Section 4.6, sorted by participant ID and visit for the SS population, along with age, sex, race, and baseline weight of the participant.

14 PHARMACOKINETICS

Pharmacokinetic analysis will be conducted outside of Avance and will be detailed in a separate Pharmacokinetic Analysis Plan.

15 IMMUOGENICITY

Immunogenicity analysis will be conducted outside of Avance and will be detailed in a separate Immunogenicity Analysis Plan.

16 CHANGES TO THE PLANNED ANALYSIS

Protocol	Key Changes
Section 13.6	The SAP has specified that treatment compliance and exposure data will be presented using only the safety analysis set (protocol specifies safety analysis set and full analysis set). This is due to all enrolled subjects having at least one dose and no difference between safety and full analysis set for this open label study.

17 INTERIM AND FINAL ANALYSIS

17.1 Interim Analysis

No formal interim analyses are planned for this study.

17.2 Final Analysis (End of Study)

The final analysis will be conducted after all participants have completed the study, the clinical database has been locked, and the analysis populations have been approved.

The final analysis will be based on the final version of the SAP. Any deviations from the planned analysis will be documented in the CSR.

18 APPENDIX 1 TIME AND EVENTS SCHEDULE

18.1 Part A (SAD)

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

18.2 Part B (MAD)

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.