Oneness Biotech Co., Ltd.

A Phase I, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Ascending Doses of Inhaled MBS-COV (SNS812) in Healthy Participants

SNS812CLCT01

Statistical Analysis Plan -Safety Part

Version: 1.0

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Abbreviations

Abbreviation	Term
ADL	Activities of Daily Living
AE	Adverse Event
AI	Aerosol Inhalation
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
ECG	Electrocardiogram
EOT	End of Treatment
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
FUV	Follow-up Visit
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HEENT	Head, Ears, Eyes, Nose, and Throat
HIPAA	Health Insurance Portability Accountability Act
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IN	Intranasal Instillation
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IS	Immunogenicity Set
LAR	Legally Authorized Representative
LDH	Lactate Dehydrogenase
LTF	Lost to Follow-up
PI	Principal Investigator
PKCS	PK concentration analysis set
PKPS	PK parameters analysis set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SRC	Safety Review Committee
SS	Safety Set
SV	Screening Visit
TEAE	Treatment Emergent Adverse Event

TV	Treatment Visit
WFI	Water For Injection

1. Introduction

This statistical analysis plan is prepared for the "A Phase I, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Ascending Doses of Inhaled MBS-COV (SNS812) in Healthy Participants" (Protocol No.: SNS812CLCT01) of Oneness Biotech Co., Ltd. In this document, the contents and methods of statistical analysis will be described in detail.

This statistical analysis plan is drafted based on protocol of SNS812CLCT01 (version 4.1, 19Jan2023*)* and Case Report Form (CRF, version 2.0, 09Jan2023).

2. Study Objectives

2.1. Part A: SAD phase

2.1.1. Primary Objectives

- To determine the safety and tolerability of MBS-COV after single doses in healthy participants.

2.1.2. Secondary Objectives

- To evaluate the pharmacokinetics (PK) of MBS-COV after single dose administration in healthy participants.
- To evaluate the immunogenicity of MBS-COV.

2.2. Part B: MAD phase

2.2.1. Primary Objectives

- To determine the safety and tolerability of MBS-COV after multiple doses in healthy participants.

2.2.2. Secondary Objectives

- To evaluate the pharmacokinetics (PK) of MBS-COV after multiple dose administrations in healthy participants.
- To evaluate the immunogenicity of MBS-COV.

3. Study Design

This is a Phase I, randomized, double-blind study designed to evaluate the safety, tolerability and pharmacokinetics (PK) of inhaled MBS-COV in healthy adult participants in the part A and part

B of the study. A total of 44 male and female healthy participants will be enrolled. All participants, after signing the Informed Consent Form (ICF), will be assessed during the screening phase. Only those participants who successfully complete the screening phase and meet the study eligibility criteria will be enrolled. MBS-COV will administered via inhalation through a portable mesh nebulizer.

3.1. Part A: SAD phase

Part A includes 3 dose-escalation cohorts (0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg MBS-COV or placebo). Each cohort will include 8 participants (6 active and 2 placebo) per below table:

Cohort	MBS-COV Does Active:placebo	Frequency of Does
A1	0.3 mg/kg (6:2)	Single Administration
A2	0.6 mg/kg (6:2)	Single Administration
A3	1.2 mg/kg (6:2)	Single Administration

From the perspective of safety, sentinel dosing will be used in each cohort, and the first 2 subjects in each cohort will be randomized 1:1 to MBS-COV or placebo. If the dose can be well tolerated for 48 hours after full administration per the study Safety Review Committee (SRC) consisting of the sponsor (designee), site Principle Investigator, and medical monitor, the remaining 6 subjects in the cohort may be randomized 5:1 to MBS-COV or placebo.

All participants will have a screening visit within 28 days of check-in (Day -1) to determine eligibility. Eligible participants will be admitted to the study center on study Day -1 at which point their eligibility to participate in the study will be confirmed. Only those participants who successfully complete the screening phase and meet the study eligibility criteria will proceed to be randomized to receive a single dose of MBS-COV or placebo in the morning of Day 1 at the assigned dose.

The decision for cohort (dose level) escalation to the higher dose levels will be made by the study SRC after safety review of available information 7-day post treatment period. The data from SAD phase will be reviewed for safety trends to start MAD phase.

3.2. Part B: MAD

This is a randomized, double-blind, placebo-controlled study in approximately 20 healthy participants. Doses will be selected based on a comprehensive review of the SAD data and estimates of the clinically efficacious dose.

The MAD Phase of the study consists of a screening period followed by multiple dose administrations of MBS-COV or placebo through a portable nebulizer once daily for 7 consecutive days (Day 1 to Day 7). Participants will be followed up for 21 days to assess post-treatment safety.

The decision for the escalation to the higher dose levels will be made by the study SRC after safety review of available information 7-day post treatment period. Each cohort will include ten participants (8 active and 2 placebo) per table below:

Cohort	MBS-COV Does Active:placebo	Frequency of Does
B1	0.6 mg/kg (8:2)	Once daily for 7 days
B2	1.2 mg/kg (8:2)	Once daily for 7 days

4. Study Outcomes Measures

4.1. Part A: SAD Phase

4.1.1. Primary Outcomes Measures

The primary outcome measures in this study are:

- Evaluation of the safety and tolerability of MBS-COV after a single administration in healthy participants. The following parameters will be used to assess safety:
    - Incidence and severity of Treatment-Emergent Adverse Events (TEAEs)
    - Incidence of withdrawals due to Adverse Events (AEs)
    - Incidence of Treatment-Related Adverse Events
    - Incidence of Serious Adverse Events (SAEs)
    - Change/shifts in laboratory values from baseline
    - Change in vital signs including blood pressure, pulse, respiratory rate, and temperature from baseline
    - Change in spirometry from baseline to assess the acute bronchospasm

- Change in other safety examination parameters from baseline

4.1.2. Secondary Outcome Measures

The secondary outcome measures in this study are:

Pharmacokinetic Outcome Measures:

- Maximum observed plasma drug concentration (C_{max})
- Apparent terminal elimination half-life ($t_{1/2}$)
- Time to maximum observed plasma drug concentration (T_{max})
- Area under the plasma drug concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (T_{last}) (AUC_{0-t})
- AUC from time 0 to infinity ($AUC_{0-\infty}$)
- Apparent plasma clearance (CL/F)

Immunogenicity Outcome Measure:

- Occurrence of anti MBS-COV antibody after administration of MBS-COV

4.2. Part B: MAD Phase

4.2.1. Primary Outcomes Measures

The primary outcome measures in this study are:

- Evaluation of the safety and tolerability of MBS-COV after multiple dose administrations in healthy participants. The following parameters will be used to assess safety:
  - Incidence and severity of Treatment-Emergent Adverse Events (TEAEs)
  - Incidence of withdrawals due to Adverse Events (AEs)
  - Incidence of Treatment-Related Adverse Events
  - Incidence of Serious Adverse Events (SAEs)
  - Change/shifts in laboratory values from baseline
  - Change in vital signs including blood pressure, pulse, respiratory rate, and temperature from baseline
  - Change in spirometry from baseline to assess the acute bronchospasm
  - Change in other safety examination parameters from baseline

4.2.2. Secondary Outcome Measures

The secondary outcome measures in this study are:

Pharmacokinetic Outcome Measures:

- Maximum observed plasma drug concentration (C_{max})
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- Time to maximum observed plasma drug concentration (T_{max})
- Area under the plasma drug concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (T_{last}) (AUC_{0-t})
- AUC from time 0 to infinity ($AUC_{0-\infty}$)
- Apparent plasma clearance (CL/F)
- Estimate of steady state Pharmacokinetic Parameters such as $AUC_{0-\tau}$, and $C_{max,ss}$, $C_{min,ss}$, C_{avg}, T_{max}, $t_{1/2}$, AUC_{tau}, λ_z, CL_{ss}/F, V_{ss}/F, DF, AR_{AUC}/AR_{Cmax} (accumulation ratio) for multiple dose administration of MBS-COV

Immunogenicity Outcome Measure:

- Occurrence of anti MBS-COV antibody after administration of MBS-COV

4.3. Study Safety Outcome Measures

4.3.1. Adverse Events

Adverse Events (AE)

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the participant to have occurred, or a worsening of a pre-existing condition. An adverse event may or may not be related to the study treatment.

AEs will be elicited through direct questioning and participant reports. Any abnormality in physical examination findings or laboratory results that the investigator believes is clinically significant (CS) to the research participant and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should not be recorded as an AE.

Serious Adverse Events (SAE)

A SAE is defined as any AE that:

- Results in death
- Is life threatening (the participant is at immediate risk of dying from the adverse experience)
- Requires participant hospitalization or prolongs existing hospitalization

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse effect when, based upon appropriate medical judgment, they may jeopardize the participant or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Treatment - Emergent Adverse Event (TEAE)

Any adverse event which occurs on or after the first administration of study drug are defined as TEAE, namely if date/time of AE occurrence is greater or equal to the date/time of first dose, those AEs will be judged as TEAE (rising grade in severity will be recorded as a new AE in CRF). For this study, AE will be collected start from the first study drug administration. Therefore, all AEs will be TEAEs.

AE Leading to Treatment Discontinuation

In this study, these AEs caused subject treatment discontinuation.

AE Leading to Death

In this study, these AEs caused subject death.

Treatment Related Adverse Event

The PI's (or designee's) assessment of an AE's relationship to study drug is part of the documentation process. The evaluation of relationship is based on the following 5 levels: Definitely related, Probably related, Possibly related, Unlikely related, Unrelated and will be recorded on CRF. The adverse events been evaluated the relationship to drug as Definitely related, Probably related, Possibly related will be referred to treatment related adverse event. The detailed definition and guidelines of 5 level relationship (Definitely related, Probably related, Possibly related, Unlikely related, Unrelated) of adverse event to study drug can be referred on protocol section 9.2.3.

Grading AE by Severity

According to the guideline of "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" issued by FDA, the severity of adverse events occurred in this study will be graded. The general guidelines for assessing the AE

grade refer on protocol appendix 1.

4.3.2. Other Safety Endpoints

Clinical laboratory test, physical examination, 12-lead ECG, vital sign assessments will be collected and analyzed to evaluate the safety of MBS-COV.

Laboratory evaluation

Clinical Laboratory Assessments are listed below:

Biochemistry	Total bilirubin (mg/dL), Alkaline Phosphatase (ALP) (U/L), Aspartate Aminotransferase (AST) (or SGOT) (U/L), Alanine Aminotransferase (ALT) (or SGPT) (U/L), Total Protein (g/dL), Albumin (g/dL), Lactate Dehydrogenase (LDH) (U/L), Amylase (U/L), Lipase (U/L), Serum creatinine (mg/dL), eGFR(ml/min/1.73 m2), Sodium (mEq/L), Potassium (mEq/L), Chloride (mEq/L), Calcium (mg/dL), Bicarbonate (mEq/L), Glucose, Random (mg/dL), Creatine kinase (U/L), Triglyceride (TG) (mg/dL), Total Cholesteriol (TC) (mg/dL)
Hematology	Hemoglobin (g/dL), Hematocrit (%), RBC/Erythrocytes (10^12/L), WBC/Leukocytes (10^6/L), Absolute Neutrophil Count (10^6/L), Platelets (10^9/L), Neutrophils (%), Lymphocytes (%), Monocytes (%), Eosinophils (%), Basophils (%)
Coagulation test	Prothrombin time (PT), Activated partial thromboplastin time (APTT), Thrombin time (TT), Fibrinogen (FIB)
Urinalysis	pH, Specimen Appearance, Color, Specific Gravity, Ketones, Bilirubin, Occult Blood, Glucose, Protein, Nitrite, Urobilinogen (mg/dL), Leukocyte, Esterase

Besides, pregnancy test will be conducted in serum. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Results of Clinical Laboratory Assessments at each scheduled visit will be recorded on the CRF.

Physical examination

The physical examination will include routine examinations for the following:

- Constitutional/General Appearance
- Head, Ears, Eyes, Nose, Throat (HEENT)
- Neurologic

- Chest (including heart and lung)
- Abdomen
- Musculoskeletal and Extremities
- Dermatologic
- Lymphatic
- Psychiatric

Any findings made during the physical examination must be noted regardless of whether they are part of the subject's medical history.

Results at each scheduled visit will be recorded on the CRF.

12-lead ECG

12-lead ECG will include ventricular rate, PR interval, QRS interval, QT interval, and QTc interval and clinical overall evaluation.

Results at each scheduled visit will be recorded on the CRF.

Vital sign

The following vital signs will include Systolic and Diastolic Blood Pressure, Pulse, Respiratory Rate, Oral Temperature and clinical overall evaluation.

Results at each scheduled visit will be recorded on the CRF.

Spirometry assessment

Spirometry assessment will include FEV1%, FEV1/FVC, PEF.

Results at each scheduled visit will be recorded on the CRF.

4.3.3. Demographics and Baseline Characteristics

Subjects' age (in years, at time of signing informed consent), gender, race, ethnicity, height, weight, and BMI will be recorded on CRF.

A medical history will be recorded on the CRF and will include:

- All ongoing medical conditions
- All previously resolved medical conditions that are relevant in the judgment of the Investigator
- Any prior medical conditions that have resolved within the last year

Events that emerge prior to the first treatment will be recorded in the medical history. Medical history term, duration, and status will be recorded on the CRF

4.3.4. Concomitant Medication and Procedure

All medications and therapies administered or taken by the participant beginning 14 days prior to Screening Visit and throughout the study will be recorded on the CRF. Participants must be questioned at each study visit concerning any new medications or changes in current medications including over-the-counter medication and topical medication.

For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose).
- Route of dosing
- Indication for use
- The start date
- The stop date (if medication/therapy is not ongoing).

4.3.5. Protocol Deviations

A protocol deviation is any noncompliance with the protocol or study procedures detailed in the laboratory or pharmacy manuals. The noncompliance may have been the result of action by the PI, site staff, or subject.

4.4. Study PK Endpoint

Refer to separate PK statistical analysis plan.

5. Statistical hypothesis

No formal statistical hypothesis for this Phase I study.

6. Analysis Datasets

The following datasets for analysis will be used in this study:

- **Full Analysis Set (FAS):** FAS includes all randomized participants. This analysis set will be used to analyze the disposition, demographic and baseline characteristics of the subjects.
- **Safety Analysis Set (SS):** SS includes all the participants who receive the study drug at least once. This population will be used for the analysis of safety parameters.

- **Pharmacokinetic Concentration Analysis Set (PKCS):** PKCS includes all randomized participants who receive at least one dose of the study drug and have at least plasma concentration. The PKCS will be used for PK concentration analysis.
- **Pharmacokinetic Parameter Analysis Set (PKPS):** PKPS includes all randomized participants who receive at least one dose of the study drug with no major protocol violations or protocol deviations that have a significant impact on PK parameters (C_{max}, AUC, etc.), and have at least one analyzable PK parameter. The PKPS will be used for PK parameters analysis.
- **Immunogenicity Set (IS):** The IS includes all randomized participants who receive at least one dose of the study drug, and have at least one ADA concentration. The IS will be used for immunogenicity analysis.

Safety analysis will be based on the safety analysis set. The division of the analysis population will be determined before database lock.

7. Statistical Methods

7.1. General Statistical Consideration

If no other specified, SAS® (Version 9.4 or above) statistical software will be used for all statistical calculation and all analyses of safety part.

All summaries will be provided by treatment group for both study parts. Continuous variables will be summarized using descriptive statistics including number of observations (n), mean, standard deviation, median (med), minimum (min) and maximum (max). Categorical variables will be summarized using frequency and percentages.

For laboratory examination, keep 2 decimal places for mean, minimum, median, and maximum, 3 decimals for standard deviation. For percentage, keep 1 decimal place.

If no other specified, baseline of safety analysis is defined as the last effective assessment record before first treatment dosing.

7.2. Data Handling

7.2.1. Missing Data

Data evaluation will be based on the data collected by CRF without any imputation for safety part. If the categorical data is missing, it can be recorded as “missing” or “unknow”.

The missing date of AE will be imputed as follows. The imputation of missing date of AE is only used to classify AEs, and the original missing date record will still be presented when generating the listing of AE related data.

- If the start date of AE was missing

1) If year and month were known and earlier than that of the first treatment dose, then impute with the last day of the known month.

2) If the year and month were known as same as that of the first treatment dose, then impute the start date with the date of first treatment dosing (date in form of "XXX(Day)XXX(Month))".

3) If year and month were known and later than that of the first treatment dosing, then impute with the first day of the known month.

4) If year only was known and earlier than that of the first treatment dosing, then impute date with "31Dec".

5) If year only was known and equal to that of the first treatment dosing, then impute the start date of AE as the first treatment dosing date (date in form of "XXX(Day)XXX(Month))".

6) If year only was known and later than that of the first treatment dosing, then impute with "1st JAN".

7) If year, month and day were all missing, use the first treatment dosing date as the start date of AE.

8) Other conditions will be regarded as missing.

- If the end data of AE was missing

1) If year and month were known, then impute with the last day of the known month.

2) If year only was known, then impute with "31Dec".

3) the start date was later than the end date after imputation, then use the start date directly as the end date.

4) Other condition will be regarded as missing.

7.2.2. Derivation and Transformation on Data

Apart from the calculation of study endpoints mentioned in section 4, which are based on data collected via CRF, no derivation or transformation will be done for data. Outliers will be reported to data management function as data issue to be resolved or confirmed before database lock. No other special data handling will be done.

7.2.3. Handling PK data

For PK data handling, please refer to separate PK statistical analysis plan.

7.3. Study Subjects

7.3.1. Subjects Disposition

The frequency counts of subjects who signed the informed consent will be calculated, distinguishing those screen failures. Listing will be provided for subjects who were failed to screen with detail reasons.

Based on all subjects receiving randomization, the frequency counts and percentage of subjects who dosed, completed the study and withdrew early, as well as the frequency counts and percentage of subjects who withdrew early for various reasons, will be calculated and summarized.

Based on full analysis set, the frequency counts and percentage of subjects included in the full analysis set, safety analysis set will be calculated and summarized.

7.3.2. Protocol Deviations

Based on full analysis set, by-subject listing of all protocol deviation will be produced.

7.3.3. Demographics and Baseline Characteristics

All demographics and baseline characteristics analysis will be performed based on the full analysis set.

Descriptive statistical summary will be performed by treatment group on demographic data collected including age (in years, at time of signing informed consent), gender, race, ethnicity, height, weight, BMI, and smoking history.

Listing by subjects will be produced regarding to baseline demographic information collected.

Medical history collected will be coded by MedDRA (version refer to DMP).

Listing will be produced by subject for recording medical history, start data, end data of treatment, and current medication.

7.3.4. Prior/Concomitant Medication and Procedures

Analysis will be performed based on safety analysis set.

Prior/concomitant medications will be coded using the latest available WHO Drug Reference Dictionary (version refer to DMP).

All prior/concomitant medication data will be provided in listing by subject in detail, as well as prior/concomitant procedure.

7.4. Safety Analysis

All safety analysis will be performed based on the safety analysis set.

Safety endpoint includes adverse events, clinical laboratory evaluations, physical examination, 12-Lead ECG, and vital signs.

7.4.1. Drug Exposure

Exposure to treatment will be summarized descriptively, and compliance on treatments for both active and placebo will be evaluated.

Listing by-subject will be produced for recording drug administration, including the date and time of administration.

7.4.2. Adverse Events

All AEs will be coded and classified according to the MedDRA (version refer to DMP) with System organ class (SOC) and Preferred Term (PT).

Frequencies and percentages of subjects and frequencies of events by treatment group for all adverse events will be summary as following:

- Summaries of all AE
- Summaries of all AE by SOC and PT
- Summaries of all SAE by SOC and PT
- Summaries of all Treatment related Adverse Event by SOC and PT
- Summaries of all AE leading to early discontinuation by SOC and PT
- Summaries of all SAE leading to early discontinuation by SOC and PT
- Summaries of all Treatment related Adverse Event leading to early discontinuation by SOC and PT
- Summaries of all AE by SOC and PT and the Worst Severity
- Summaries of all Treatment related Adverse Event by SOC and PT and the Worst Severity

Listing by subjects will be provided for all AEs, SAE, Treatment related Adverse Event.

7.4.3. Laboratory Evaluations

Clinical laboratory evaluations include Hematology, Blood chemistry, Urinalysis, Coagulation test.

Laboratory evaluation results of each visit and their changes from baseline will be calculated and summarized in descriptive statistics by treatment group.

Listing by subjects and evaluations will be produced for results from visits and timepoints.

Any abnormal with clinical significance results will be tabulated.

The results of pregnancy test of female subjects will be tabulated.

7.4.4. Physical Examination

Listing by subjects will be produced for all the physical examination results at baseline and each post-baseline visit timepoint.

7.4.5. 12-Lead ECG

12-lead ECG assessment results of each visit and their changes from baseline will be calculated and summarized in descriptive statistics by treatment group.

Listing by subjects will be produced for all 12-lead ECG result. Abnormal with clinical significance results of 12-lead ECG will be provided by listing separately.

7.4.6. Vital Signs

Vital signs results of each visit and their changes from baseline will be calculated and summarized by treatment group.

Listing by subject will be provided for all vital signs results. Abnormal with clinical significance results of vital signs will be provided by listing separately.

7.4.7. Spirometry Assessment

Spirometry results of each visit and their changes from baseline will be calculated and summarized by treatment group.

Listing by subject will be provided for all spirometry assessment results. Abnormal with clinical significance results of spirometry assessment will be provided by listing separately.

7.5. PK analysis

For study PK analysis, please refer to separate PK statistical analysis plan.

8. Reference

[1] National Medical Products Administration, Guidance of Data Management and Statistical Analysis Plan for Clinal Trials, 2021.

[2] National Medical Products Administration, Guidance of Biostatistics for Clinical Trials, 2016.