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

Protocol Number:	**SNS812CLCT01**
Version:	**V4.1**
Date:	**19-Jan-2023**
ClinicalTrials.gov ID:	**NCT05677893**

Sponsor: **Oneness Biotech Co., Ltd.**
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Confidentiality Statement

SPONSOR SIGNATURE PAGE

Protocol Title	**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 Number	**SNS812CLCT01**
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Protocol (v4.1) accepted and approved by:

Oneness

Director/ Department of Pharmaceutical Development

Oneness Biotech Co., Ltd. (Oneness)

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Signature_____ Date_____

INVESTIGATOR SIGNATURE PAGE

Protocol Number:	**SNS812CLCT01**
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I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical study. I also agree to comply with US Food and Drug Administration (FDA) regulations and Investigational Review Board/Institutional Ethics (IRB/IEC) requirements for testing on human participants. I agree to ensure that the requirements for obtaining informed consent are met.

Principal Investigator's Signature _____ Date _____

Print Name _____

Site Number _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Oneness Biotech Co., Ltd.	
Name of Study Product: MBS-COV(SNS812) **Comparator Product:** Placebo (Normal Saline)	
Protocol Number: SNS812CLCT01	**Indication:** Coronavirus Disease 2019 (COVID-19)
Title of Study: 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	
Study Center: One center in the United States (US)	
Planned Number of Participants: 44 participants	**Study Development Phase:** Phase I
Indication for Use: MBS-COV is indicated for patients with mild to moderate COVID-19	

Study Objectives

Primary Objective:

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

Secondary Objective:

- To evaluate the pharmacokinetics (PK) of MBS-COV after single dose administration (Part A) and multiple dose administrations in healthy participants (Part B).
- To evaluate the immunogenicity of MBS-COV.

Study Outcome Measures

Primary Outcome Measures:

The primary outcome measures in this study are:

- Evaluation of the safety and tolerability of MBS-COV after a single and multiple dose administrations in healthy participants. The safety and overall tolerability assessments will be evaluated based on:
  - 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

Name of Sponsor/Company: Oneness Biotech Co., Ltd.	
Name of Study Product: MBS-COV(SNS812) **Comparator Product:** Placebo (Normal Saline)	
Protocol Number: SNS812CLCT01	**Indication:** Coronavirus Disease 2019 (COVID-19)

- Change in other safety examination parameters from baseline

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)
- 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 (ADA) after administration of MBS-COV

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.

Part A (SAD phase)

Part A is randomized, blinded study of a single ascending dose (SAD) phase to evaluate the safety, tolerability and PK of inhaled MBS-COV in healthy participants.

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.

Participants will be assigned to one of up to three doses of MBS-COV (0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg) and treated sequentially with increasing doses. Each cohort will include eight (8) participants (6 active and 2 placebo) per below table:

Table 0-1: SAD Phase Cohorts

Cohort		Number of Participants	MBS-COV Dose (mg/kg)	Frequency of Dose
SAD Phase	A1	6 (MBS-COV) +2 (placebo)	0.3	Single Administration
	A2	6 (MBS-COV) +2 (placebo)	0.6	Single Administration
	A3	6 (MBS-COV) +2 (placebo)	1.2	Single Administration

SAD phase will include a sentinel design in which 2 participants at the given cohort dose be initially enrolled. If the dose can be well tolerated for 48 hours after full administration per site Principle Investigator's judgement, the remaining 6 participants will be enrolled to receive a single dose of MBS-COV at the same dose.

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. The data from SAD phase will be reviewed for safety trends to start MAD phase.

Part B (MAD Phase)

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:

Table 0-2: MAD Phase Cohorts

Cohort		Number of Participants	MBS-COV Dose (mg/kg)	Dose
MAD Phase	B1	8 (MBS-COV) +2 (placebo)	0.6	Once daily for 7 days
	B2	8 (MBS-COV) +2 (placebo)	1.2	Once daily for 7 days

Study Visits:

- **Screening Visit** (SV: Up to 28 Days prior to Day 1): Consists of signing the ICF and study qualification based on evaluation of inclusion/exclusion criteria.
- **Treatment Visit 0** (T0: Day -1): All participants continuing to meet eligibility criteria will be enrolled into the study and confined to research clinic until Day 2 for cohort A1 to A3 (SAD phase) and Day 9 for cohort B1 to B2 (MAD phase).
- **Treatment Visit 1: Baseline Visit** (T1: Day 1)**:** The first assigned study treatment dose will be administered after completion of all study evaluations. Adverse events and changes in concomitant medications will be collected. Participants in Cohorts A1 to A3 will inhaled a single dose of MBS-COV or placebo through a portable nebulizer on Day 1. Participants in cohort B1 and B2 will receive doses of MBS-COV or placebo by through a portable nebulizer once daily for 7 consecutive days from Day 1 to Day 7.

Part A (SAD Phase)

  - **Treatment Visit 2** (T2: Day 2)
  - **Treatment Visit 3** (T3: Day 3)
  - **Treatment Visit 4** (T4: Day 4)
  - **Treatment Visit 5 (End of Treatment)** (T5: Day 7)
- **Follow-Up Visit 1 (FU1: Day 14)**
- **Follow-Up Visit 2 (FU2: Day 28)**

Part B (MAD Phase)

  - **Treatment Visit 2** (T2: Day 2)
  - **Treatment Visit 3** (T3: Day 3)
  - **Treatment Visit 4** (T4: Day 4)
  - **Treatment Visit 5** (T5: Day 5)
  - **Treatment Visit 6** (T6: Day 6)
  - **Treatment Visit 7** (T7: Day 7)
  - **Treatment Visit 8 (**T8: Day 8)
  - **Treatment Visit 9 (End of Treatment) (**T9: Day 9)
- **Follow-Up Visit 1** (FU1: Day 14)

- **Follow-Up Visit 2** (FU2: Day 28)

If any of the dose escalation stopping criteria have occurred in Part A or Part B, the SRC will make a final recommendation for dose escalation to the next cohort.

NOTE: The dose escalation decision through the study will not be made until the following:

(1) All study participants in a given cohort have been enrolled,

(2) All such participants have completed Treatment Visit 5 (Day 7) (for SAD-Part A) and Treatment Visit 9 (Day 9) (for MAD-Part B) of the study or withdrawn from the study, whichever occurs first.

(3) The SRC will review the available safety data and recommend further dose escalation.

Additionally, dose escalation stopping criteria are defined per the below:

a. Death in any participant in which the cause of death is judged to be possibly, probably or definitely related to MBS-COV.

b. The occurrence in any participant of a severe local application site reaction (Grade 3 which doesn't resolve or recurs; or Grade 4) that is judged to be possibly, probably or definitely related to MBS-COV.

c. The occurrence in any participant of a SAE whose causal relationship to MBS-COV is judged to be probably, possibly, or definitely related to MBS-COV.

d. The occurrence, in two or more participants of Grade 3 AE or laboratory abnormalities, judged to be probably, possibly, or definitely related to MBS-COV.

e. The occurrence of two of the same AE or laboratory abnormality ≥ Grade 3 judged to be probably, possibly, or definitely related to MBS-COV.

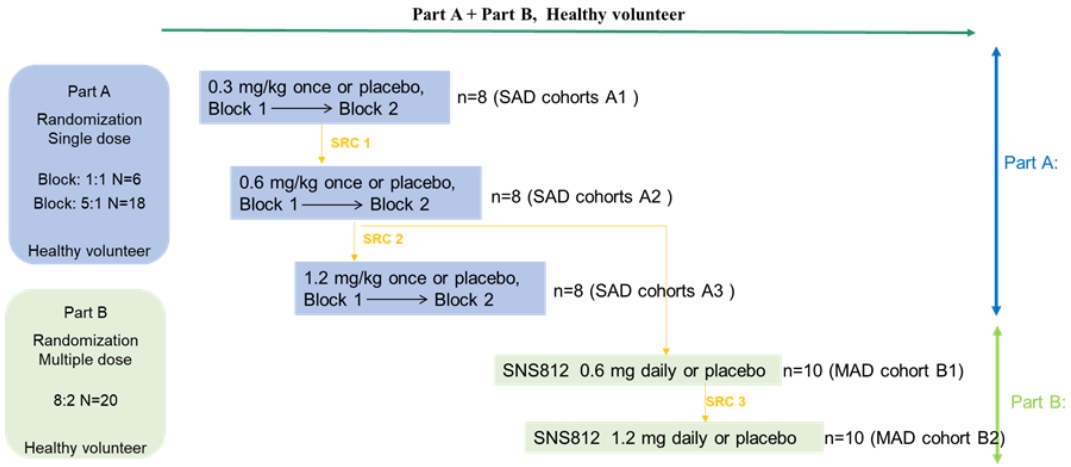
f. The occurrence, in one or more participants of Grade 4 AE or laboratory abnormalities, judged to be probably, possibly, or definitely related to MBS-COV.

g. Any pattern of significant symptoms, physical findings, or laboratory abnormalities that, although individually minor, collectively represent a safety concern in the opinion of the investigator and are judged by the SRC to be at least possibly related to MBS-COV.

h. PK exposure limits of mean AUC of 385.6 h*ng/mL or C_{max} of 141.8 ng/mL for one cohort, whichever comes first.(Single dose: AUC of 386.9 h*ng/mL or C_{max} of 91.7 ng/mL)

The SRC will review the PK data (if applicable) and safety trends of available information 7-day post treatment period of Cohort A1 and A2 (or if study stops prematurely due to safety reasons), to start part B of the study. The starting dose of Part B will be determined by SRC.

Figure 0-1: Dose Escalation Schematic



Blood Sample Collection for the PK study:

- SAD cohorts A1 to A3: For the single dose on day 1, blood samples will be collected before dosing, and afterwards at 5 min (± 1 min), 15 min (± 2 min), 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 4 h (± 5 min), 8 h (± 10 min), 10 h (± 10 min), 24 h (± 10 min) and 48 h (± 10 min) (Total 11 samples) after dosing.
- MAD cohort B1 and B2: Blood samples will be collected on Day 1 and Day 7 before dosing, and afterwards at 5 min (± 1 min), 15min (± 2 min), 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 4 h (± 5 min), 8 h (± 10 min), 10 h (± 10 min) on Day 1; and at 5 min (± 1 min), 15min (± 2 min), 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 4 h (± 5 min), 8 h (± 10 min), 10 h (± 10 min) , 24 h (± 10 min) and 48 h (± 10 min) after dosing on Day 7; and before dosing on Day 2 to Day 6 (Total 25 samples). The detailed study schedule and assessments in each visit are provided in Section 4 of the protocol.

Blood Sample Collection for the immunogenicity study:

- Blood Sample will be collected on Day 1 before dosing, Day 14 and Day 28 for SAD and MAD cohorts, and the analysis will be performed when analytic method is well-established.

Study Duration:

Part A

SAD Phase:

- Screening Period (For SAD Phase Only): Up to 28 days
- Treatment Period: 7 days
  - In-unit: 3 day
- Follow-Up Period: Up to 21 days
- **Total Study Duration**: Up to 56 days

Part B

MAD Phase:

- Screening Period: Up to 28 days

- Treatment Period: 9 days
  - In-unit: 9 days
- Follow-Up Period: Up to 19 days after EOT
- **Total Study Duration**: Up to 56 days

Eligibility Criteria

Inclusion Criteria:

Participants will be eligible for enrollment in the study only if they meet ALL the following criteria at time of Screening:

1. Male or female adults who are between 18 and 55 years old (inclusive).
2. Body mass index (BMI) between 18.0 and 32.0 kg/m^2 (inclusive).
3. No serious or chronic underlying disease which would adversely affect the study conduct and data interpretation per the investigator.
4. Female participants should have negative results in serum pregnancy test at screening and negative urine pregnancy test at admission (Day -1).
5. Participants with normal spirometry (FEV1 %: 80 % or greater) results at screening or day -1.
6. Both male and female participants and their partners of childbearing potential must agree to use two medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], or one of the following methods of birth control (intrauterine devices, tubal sterilization or vasectomy) or must practice complete abstinence from intercourse of reproductive potential from study entry to 3 months after the last day of treatment (excluding women who are not of childbearing potential and men who have been sterilized).
7. Participants should have normal (or abnormal but not clinically significant) laboratory results per the PI's judgement including the hematology, biochemistry, coagulation indices and urinalysis
8. Participants should have a normal (or abnormal but not clinically significant) 12-lead ECG at screening and day -1 and chest X-ray at screening
9. Participants should be willing to cooperate and able to participate in this study, comply with all protocol requirements, and sign an informed consent.
10. Current non-smokers and those who have not smoked within the last 3 months. This includes the use of cigarettes, e-cigarettes, and nicotine replacement products.
11. Nasopharyngeal or nasal swab sample of Participants collected for COVID-19 antigen rapid test at screening and qRT-PCR test on Day -1 should be negative.

Eligibility Criteria

Exclusion Criteria:

Participants meeting ANY of the following criteria at time of Screening will be excluded from enrollment:

1. The participant has a known history of, or a positive test result for, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at screening.
2. As reported by the participant has severe cardiovascular disease, neurological disease, hematological disease, infectious disease, mental disorder, liver disease, gastrointestinal disease, lung disease, endocrine disease, immune disease or kidney disease, or has a history of the above diseases, or other symptoms known to interfere with the absorption, distribution, metabolism, or excretion of the medicine, or other conditions that the investigator believes will increase the risk

of the participant and might interfere with the study conduct and results interpretation

3. The participant has history or presence of active lung disease (i.e., asthma, chronic obstructive pulmonary disease [COPD], pulmonary fibrosis, hemoptysis, bronchiectasis) or prior intubation due to respiratory failure conditions.
4. The participant has upper respiratory infection within the 3 months prior to the first dose of study drug.
5. Consumed more than 14 units of alcohol per week in the 6 months before screening (1 unit of alcohol = 360 mL of beer or 45 mL of spirits with 40% alcohol content or 150 mL of wine) or have taken alcohol products in the 48 hours prior to administration, or those who have a positive alcohol breath test result at screening and day -1.
6. Unwillingness to abstain from the consumption of any caffeine or alcohol-containing food or drinks that may influence the drug metabolism from 48 hours before administration.
7. History of drug abuse or a positive drug abuse (barbiturates, methamphetamine, benzodiazepines, morphine/opiates, phencyclidine (PCP), amphetamines, tetrahydrocannabinol (THC), methylenedioxymethamphetamine (MDMA), cocaine, methadone, and cotinine) test result at screening and day -1.
8. Female participants who are lactating.
9. Use of prescription or non-prescription drugs, including vaccine within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study drug.
10. The subject has received an experimental agent (vaccine, drug, biologic, device, blood product or medication) within 1 month prior to the first dose of study drug and will receive another experimental agent during the duration of this study.
11. The participant has a history of frequent nose bleeding.
12. Participants with known allergic reactions to the study drug or its excipients.
13. The participant has an acute sinusitis or history of chronic sinusitis, a history of active allergic rhinitis (AR), history of perennial allergic rhinitis (PAR), or current seasonal allergic rhinitis (SAR), or recent viral rhinitis within 2 weeks prior to administration.
14. The participant has Any nasopharyngeal abnormality that may have interfered with nasal absorption, distribution, or study-related evaluations of signs or symptoms (e.g., polyps, septal deviation).
15. Blood donation of more than 400 mL within 3 months before screening or more than 200 mL within 4 weeks before screening or plan to donate blood during study period.
16. Any other clinical condition that, in the Investigator's judgment, would potentially compromise study compliance or the ability to evaluate safety/efficacy.

Statistical Considerations:

Sample Size Determination and Rationale

The sample size of 44 participants (24 healthy participants in part A and 20 healthy participants in part B) will be used in this study. This sample size is selected based on clinical judgment and not based on statistical power calculation; it is deemed adequate to provide clinically meaningful descriptive results consistent with study objectives.

Randomization and Blinding:

All eligible participants will proceed to be randomized and will be assigned the IP kit. A detailed Randomization plan the block size and all the relevant considerations will be detailed in the randomization plan. The participants will be randomized using a web-based randomization system at Treatment Visit 1 (Baseline) and site personnel will be trained on this system. Only those participants who successfully complete the screening phase and meet the study eligibility criteria will proceed to randomization.

Statistical Analysis Populations

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 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.

PK 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.

PK parameters 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.

Statistical Analysis

All collected study data will be presented in participant data listings. All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

All data collected will be summarized and analyzed according to the variable type:

- Continuous data summaries will include:
  - Number of observations, mean, standard deviation, median, and minimum and maximum values.
- Categorical data summaries will include:
  - Frequency counts and percentages.

No inferential statistics are planned.

The pharmacokinetic analyses will be performed using Phoenix® WinNonlin 8.3.1 or above.

A Statistical Analysis Plan (SAP) will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the pharmacokinetic and safety data from this study.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF 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

Abbreviation	Term
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 AND BACKGROUND

1.1. STATEMENT OF INTENT

The design, conduct, and reporting of this study shall be conducted in compliance with the protocol, International Council for Harmonisation/Good Clinical Practice (ICH/GCP), and all appropriate regulatory requirements. Investigator(s) participating in this study will have documented training in GCP. Independent monitoring of the study will be accomplished utilizing a Contract Research Organization (CRO).

1.2. BACKGROUND OF THE DISEASE

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 500 million people and caused more than 6.2 million deaths worldwide as of April 26, 2022, according to the John Hopkins coronavirus resource center. Despite the availability of vaccines, breakthrough infections caused by the variant appear to be driving a new wave of pandemic (Dyer 2021, Kupferschmidt 2021). The SARS-CoV-2 vaccines initially achieved great success in reducing viral infection and severe illness. The effectiveness of ChAdOx1 nCoV-19, BNT162b2 and mRNA-1273 vaccine reached 70.4%, 95% and 94.1%, respectively (Baden 2021, Knoll 2021, Wang 2021). Nevertheless, the emergence of new variants has raised great concerns, since reduced sensitivity of SARS-CoV-2 variants to therapeutic neutralizing antibodies, serum from convalescent patients and vaccinated individuals have been reported (Planas 2021). A report from the UK indicates that the effectiveness of two doses of ChAdOx1 nCoV-19 vaccine against delta infection reduces to 67% while BNT162b2 reduces to 88% (Lopez 2021). Another report from Qatar showed that two doses of BNT162b2 only present 51.9% of effectiveness while mRNA-1273 presents 73.1% (Tang 2021). These reports implicate those viral mutations has influenced vaccine effectiveness.

Recently, a novel variant called Omicron, is spreading rapidly across the globe. The unusual, clustered mutations and extensive transmission of this variant led the World Health Organization to designate it as a variant of concern on November 26, 2021. In total, 32 mutations were identified in Omicron's spike protein and 15 in the receptor-binding domain, which are responsible for interacting with the angiotensin-converting enzyme 2 receptor. The highly mutated features of Omicron have allowed it to escape most of the existing SARS-CoV-2 neutralizing antibodies (Cao 2021). A more than 22-fold reduction of neutralizing titers against the Omicron strain as compared to the wild-type strain was observed in individuals receiving 2-dose of mRNA vaccine, and a third dose of mRNA vaccine was suggested (Muik 2022). Moreover, an artificial intelligence model trained with tens of thousands of experimental data and extensively validated based on experimental results for SARS-CoV-2 indicated that Omicron may be over 10 times more contagious than the original virus and about 2.8 times more infectious than the Delta variant (Chen 2022). The emergence of Omicron variant indicates how fast the SARS-CoV-2 evolves, and its potential impact on the current protein-based intervention

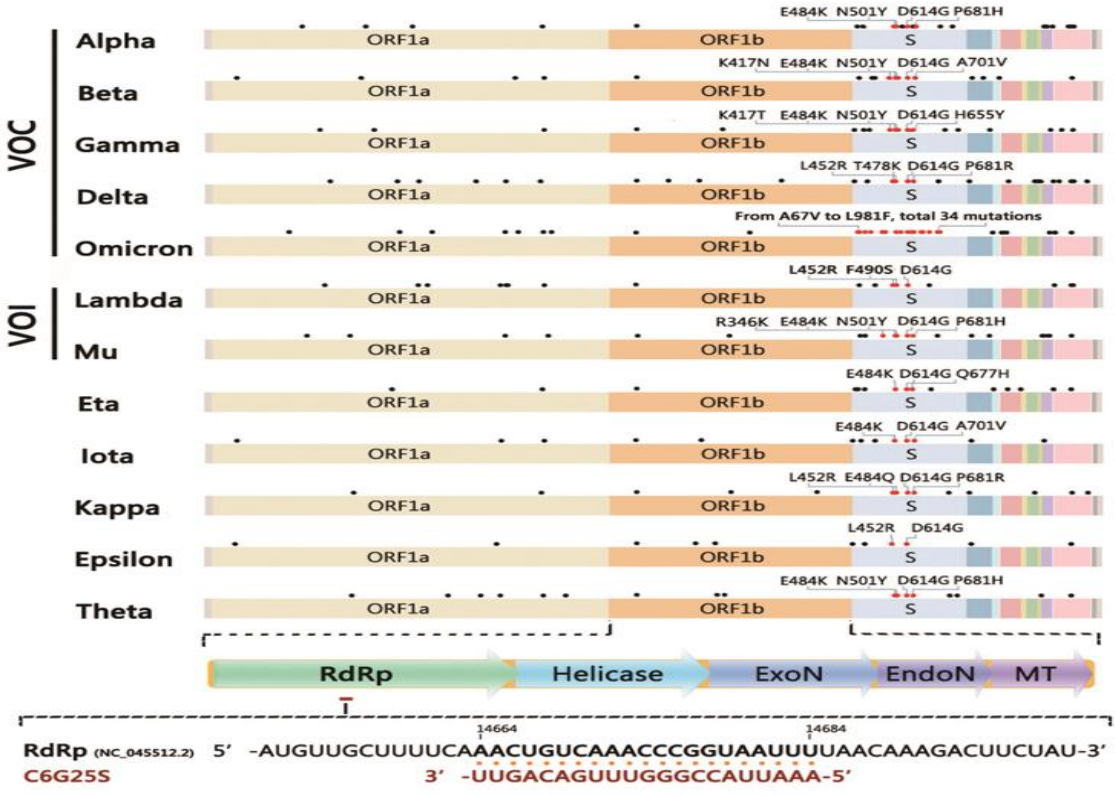
(i.e., vaccines, antibodies, or convalescent plasma) that primarily target the highly-mutated spike protein (Van 2020) cannot be neglected.

One therapeutic with great potential is short-interfering (si)RNA, which is an artificially synthesized double-stranded RNA of 19–23 nucleotides (Zamore 2000). Upon entering the cytosol, siRNA interacts with several proteins to form an RNA-induced silencing complex (RISC) and subsequently knocks down the expression of target genes based on sequence complementarity.

1.3. NAME AND DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

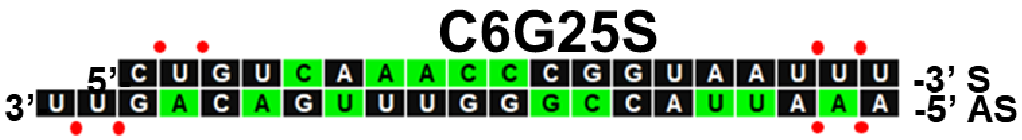
Oneness Biotech Co., Ltd is developing MBS-COV for the treatment of mild to moderage COVID-19. MBS-COV is a potent siRNA targeting a highly conserved region of RdRP gene of SARS-CoV-2. It consists of double-stranded RNA with each of 21 nucleotides in length and is fully-modified with 2'-O-methyl, 2′-fluoro or phosphonothioate (PS) substitution (Figure 1-1) shows the sequence and target site of MBS-COV. MBS-COV is a double-stranded, small interfering RNA (siRNA) targeting a highly conserved RNA-dependent RNA polymerase region of SARS-CoV-2 RNA to induce the degradation effect against the virus RNA.

Figure 1-1: Genetic Map and Locations of MBS-COV



MBS-COV (also named MBS-COV C6G25S) drug substance is the sodium salt of a chemically synthesized double-stranded oligonucleotide, with a 19-base (19-mer) sense strand and a 21 base (21-mer) antisense strand. The sequence and modification of MBS-COV is shown in Figure 1-2.

Figure 1-2: Sequence and Modification of MBS-COV(C6G25S)



1.4. SUMMARY OF PRIOR NON-CLINICAL AND CLINICAL STUDIES

1.4.1. Non-Clinical Studies

There have been multiple non-clinical studies conducted with MBS-COV to evaluate its toxicological and pharmacokinetic profile. Table 1-1 provides a summary of pre-clinical studies.

Table 1-1: Overview of Pre-Clinical Studies

Study	Summary
Primary Pharmacology	• MBS-COV inhibit viral RNA amplification with pico-molar IC_{50} (IC_{50} = 0.17 nM) • MBS-COV inhibit different variants and human coronavirus 229E with pico-molar IC_{50} (IC_{50} = 0.09 ~ 0.73 nM). • The concentration (detected via OD260) and integrity (assayed via HPLC) of MBS-COV were the same before and after nebulization • The effectiveness of the MBS-COV after nebulization was the same as that before nebulization, evaluated by the inhibition of viral envelope gene expression in Vero E6 cells. • The nebulization rate was maintained unaffected when the concentration of C6G25S was ≦30 mg/mL and reduced significantly at higher concentrations. • The C6G25S concentration in the inhalation chamber reached a maximum within 2 min and was maintained at 1.48 mg/L. • The particle size of the siRNA aerosol generated by the nebulizer had a mass median aerodynamic diameter (MMAD) of 4.845 μm, a geometric

Study	Summary
	standard deviation (GSD) of 2.402 μm with a fine particle fraction (FPF; <5 μm) of 50.22%. • MBS-COV was distributed throughout the lung in the AI group, whereas uneven distribution in the IN group. There are twice as many MBS-COV+ cells in the AI group compared with MBS-COV significantly suppresses the production of viral RNA and infectious virions in both prophylactic treatment and co-treatment of both SARS-CoV-2-and Delta-infected K18-hACE2 mice. • MBS-COV inhibits spike protein expression and prevents SARS-CoV-2-induced pathological features in lungs of K18-hACE2 transgenic mice. • MBS-COV reduces the expression of inflammatory cytokines induced by SARS-CoV-2 in lungs of K18-hACE2 transgenic mice.
Secondary Pharmacology	• Modification of MBS-COV significantly reduced off-targets. None of the off-target genes are essential for cell viability.
Safety Pharmacology	• No cytotoxicity was observed in the treatment up to 40μM of MBS-COV. • No inflammation-associated cytokines were significantly induced in MBS-COV treated-human PBMCs. • MBS-COV does not activate non-specific immune response against SASR-CoV-2 in mice treated with efficacy dose of MBS-COV. MBS-COV inhibits viral RNA amplification and infectious virion production, while control siRNA does not. The virus inhibition of MBS-COV is not evoked through nonspecific immune responses. • No significant immune stimulation was observed in mice treated with high dose (up to 75 mg/kg) of MBS-COV. • No MBS-COV-related changes in cardiovascular functions, respiratory functions, blood pressure, body temperature and clinical observation after administration up to the highest dose of 16+30

Study	Summary
	mg/kg (AI+SC).
Pharmacokinetics	**Lung distribution and pharmacokinetics of MBS-COV in lungs of golden hamsters** • In a single inhalation of MBS-COV at delivered doses of 15.7 and 52.7 mg/kg, MBS-COV level in lungs of golden hamsters peaked at 0.5-1 hr postdose. • The elimination $T_{1/2}$ ranged 60.95 -74.16 hours in low dose group and 152.20 - 182.59 hours in high dose group. • The C_{max} were within 28.98 -30.79 μg/g lung in low dose group and 64.30 - 108.77 μg/g lung in high dose group. • No significant gender difference was found. • The maximum concentrations in lung tissue and the systemic exposures to MBS-COV were positively correlated with the administrated doses. **Toxicokinetics of MBS-COV in the blood of golden hamsters** • In the 7-day repeat-dose toxicokinetic study, the actual delivered doses were 30 and 90.4 mg/kg for medium and high dose group. The elimination $T_{1/2}$ values ranged from 1.97 to 17.42 hours for sense and antisense strand of MBS-COV in medium and high dose group on Day 1. On Day 7, $T_{1/2}$ values ranged from 1.88 to 6.06 hours. Mean C_{max} and AUC_{last} values increased with the increasing administered doses. MBS-COV did not accumulate in golden hamsters, and there was no significant gender difference. • In the 14-day repeat-dose toxicokinetic study, the actual delivered doses were 57 and 87.9 mg/kg for medium and high dose group. The elimination T1/2

Study	Summary
	values ranged from 1.18 to 36.67 hours on day 1 for sense and antisense strand of MBS-COV in medium and high dose group. On day 14, T1/2 values ranged from 3.47 to 9.02 hours. Mean Cmax and AUClast values increased with increasing administered doses in both females and males. There was no significant gender difference. No accumulation was observed in male animals; in female animals, a tendency of accumulation was observed in the medium group. No accumulation was observed in the high dose group.
Toxicology	**Single Dose** • MBS-COV was well-tolerated in SD rat at intranasal instillation of 20, 40, and 75 mg/kg and the NOAEL was considered to be 75 mg/kg.
	Repeat Dose • MBS-COV was well-tolerated in CD-1 (ICR) mice at intranasal instillation of 2, 10, and 50 mg/kg and the NOAEL was considered to be 50 mg/kg. • MBS-COV was well-tolerated in Golden hamster at inhalation of 10, 30, and 90 mg/kg and the NOAEL was considered to be 90 mg/kg. • MBS-COV was well-tolerated in Golden hamster at inhalation of 18, 57, and 87.9 mg/kg. Minimal to slight alveolar macrophage aggregation in the lung with bronchi was observed in medium- and high-dose group, and could be completely recovered after a 1-week recovery period. no obvious systemic toxicity and toxic target organs were found at doses of ≤ 87.925±21.984 mg/kg. The NOAEL was considered to be 87.9 mg/kg.
	Genotoxicity • The bone marrow micronucleus analysis showed that the incidence of micronucleus in the positive control group increased significantly compared with the vehicle control group, while the incidence of

Study	Summary
	micronucleus in all MBS-COV treatment groups did not. No genotoxicity was observed for MBS-COV to damage chromosome in bone marrow erythrocytes when CD-1 (ICR) mice were administered with MBS-COV at doses up to 2000 mg/kg by intravenous injection for 2 consecutive days. • The potential of MBS-COV to cause chromosome aberration was evaluated by using Chinese Hamster Lung (CHL) Fibroblast continuously exposed (for either 4 or 24 hours) to different concentrations of MBS-COV with or without S9 metabolic activation. The chromosomal aberration rates in CHL cells treated with MBS-COV at all tested concentrations for 4 hours with or without S9 and 24 hours without S9 showed no significant difference (P>0.05) when compared with the vehicle control group. The results indicate that MBS-COV at doses ≤500 μg/mL, regardless of the presence or absence of the metabolic activation enzyme system, has no genotoxic potential to induce chromosome aberration. • The mutagenicity study was conducted at dose levels of 50, 150, 500, 1500 and 5000 μg/plate of MBS-COV in both the absence and presence of S9 activation incubated with *Salmonella typhimurium* tester strains for 65.5 hours. Compared with the spontaneous control group, the revertant colony counts of TA97a, TA98, TA100, TA102 and TA1535 strains in all the dose groups when treated with or without S9 were within the negative historical background range. MBS-COV at concentrations ⩽5000 μg/plate is not mutagenic in the presence or absence of metabolic activation. **Systemic Anaphylaxis Study** • MBS-COV did not exert any systemic anaphylaxis response in Guinea Pigs, and therefore is not considered a sensitizer.

1.4.2. Clinical Studies

The current proposed study is a first-in-human study to evaluate the safety, tolerability, and PK of inhaled MBS-COV.

1.5. RISKS / BENEFITS ASSESSMENT

1.5.1. Systemic Anaphylaxis

The potential of MBS-COV to provoke respiratory sensitization reactions was evaluated in Hartley guinea pigs (n = 9 per groups). Three sensitization inductions with either MBS-COV (actual delivered doses of 3.8 and 15.1 mg/kg) or vehicle control (saline) were performed by inhalation every other days (Day 1, 3 and 5), followed by a challenge of MBS-COV (actual delivered doses of 8.1 and 32.6 mg/kg) by inhalation at two or three weeks after the last induction (Day 19 or 26). After challenged, the animals were observed for multiple symptoms for 3 hours. In conclusion, MBS-COV did not exert any systemic anaphylaxis response in Hartley guinea pigs, and therefore is not considered as a sensitizer.

1.5.2. Pregnancy

To date, no carcinogenicity and reproductive studies have been conducted with MBS-COV. Risks to unborn babies are unknown at this time, thus pregnant females will be excluded from this study. Females of childbearing potential must have a negative pregnancy test prior to enrollment and must agree to use appropriate birth control methods throughout the study duration (excluding women who are not of childbearing potential).

1.5.3. Venipuncture for Blood Sampling

Venipuncture for blood sample collection carries a minimal risk of minor discomfort and the possibility of minor bruising at the site of the needle puncture and, rarely, the possibility of infection at the needle puncture site.

1.5.4. Unknown Risks

As with all research there is the remote possibility of risks that are unknown or that cannot be foreseen based on current information.

1.6. RATIONALE FOR STUDY DOSE

Golden hamster was well-tolerated at inhalation doses of 10, 30, and 90 mg/kg of MBS-COV once daily for 7 days in the dose ranging finding (DRF) study and 18, 57, and 87.9 mg/kg for 14 days in the GLP compliance study. There were no MBS-COV-related clinical observations or toxicology effects on body weights, food intake, hematology, serum biochemistry, urinalysis and histopathology. No obvious systemic toxicity and toxic target organs were found at doses of $\leqslant$ 87.9 mg/kg. The NOAEL was considered to be 87.9 mg/kg.

For inhaled drug, clinical doses will need to be supported by both local and systemic safety margins. The pulmonary deposition factor (10% for hamster) was considered in the calculations for systemic safety. Based on the calculation (based on 1.2 mg/kg as human dose) shown as below, for the first in human starting dose (0.3 mg/kg) and maximum dose (1.2 mg/kg), the safety margin of systemic toxicity is 3.809 and 0.952, respectively. And the safety margin of local toxicity is 83.89 and 20.97, respectively. As no evidence of unmonitorable systemic toxicity in preclinical studies, proposed clinical doses up to 1.2 mg/kg would have adequate nonclinical support.

Determining PDDs in rats and humans：

Assuming the NOAEL for local is the same with the NOAEL for systemic effects in the hamster study, 87.9 mg/kg/d.

PDD $_{\text{hamster local}}$ = 87.9 mg/kg/d *0.1(DF)=8.79 mg/kg/d

PDD $_{\text{hamster system}}$= 87.9 mg/kg/d *0.1(DF)=8.79 mg/kg/d

PDD $_{\text{human}}$=1.2 mg/kg subject/d* 1 (DF)= 1.2 mg/kg/d

- Determining lung doses in rats and humans

PDD $_{\text{hamster, lung}}$=8.79 mg/kg/d* 0.12 BWT/0.7g (lung hamster) =1.51 mg/g lung

PDD $_{\text{human, lung}}$=72 mg/d /1000 g lung hamster=0.072 mg/g lung

- Calculating SM for systemic effects:

SM $_{\text{system}}$=8.79 mg/kg/d (hamster)*0.13（HED）/ 1.2 mg/kg/d (human) =0.952

- Calculating SM for local effects

On a mg/g lung/day basis: SM $_{\text{local}}$=1.51mg/g /0.072 mg/g =20.97

Since the safety profile of MBS-COV in humans is unknown and this is the first clinical study to assess MBS-COV in humans, phase I clinical study for MBS-COV will be divided into two parts. Part A is a randomized, double-blind, and placebo-controlled study with single ascending dose (SAD) design of inhaled MBS-COV in healthy participants for determining safety, tolerability, and pharmacokinetics of MBS-COV. Part B will be performed after review of sufficient result of Part A. Part B is a randomized, double-blind and placebo-controlled study with multiple ascending doses (MAD) of inhaled MBS-COV in healthy participants to evaluate safety, tolerability, and pharmacokinetics.

2. STUDY OBJECTIVES AND ENDPOINTS/OUTCOME MEASURES

2.1. STUDY OBJECTIVES

2.1.1. Primary Objective

The primary objective of this study is:

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

2.1.2. Secondary Objective

The secondary objectives of this study are:

- To evaluate the pharmacokinetics (PK) of MBS-COV after single dose administration in healthy participants (Part A) and multiple dose administrations in healthy participants (Part B).
- To evaluate the immunogenicity of MBS-COV.

2.2. STUDY OUTCOME MEASURES

2.2.1. Primary Outcome Measures

The primary outcome measures in this study are:

- Evaluation of the safety and tolerability of MBS-COV after a single and 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

2.2.2. Secondary Outcome Measures

The secondary outcome measures in this study are:

<u>Pharmacokinetic Outcome Measures:</u>

- 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)
- 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

3. STUDY DESIGN

3.1. GENERAL SCHEMA

This is a Phase I, randomized, double-blind study designed to evaluate the safety, tolerability, and 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 nebulizer.

Part A (SAD phase)

Part A is randomized, blinded study of a single ascending dose (SAD) phase to evaluate the safety, tolerability and PK of inhaled MBS-COV in healthy participants.

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.

Participants will be assigned to one of up to three doses of MBS-COV (0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg) to be treated sequentially with increasing doses. Each cohort will include eight (8) participants (6 active and 2 placebo) per below table:

Table 3-1: SAD Phase Cohorts

Cohort		Number of Participants	MBS-COV Dose (mg/kg)	Frequency of Dose
SAD Phase	A1	6 (MBS-COV) +2 (placebo)	0.3	Single Administration
	A2	6 (MBS-COV) +2 (placebo)	0.6	Single Administration
	A3	6 (MBS-COV) +2 (placebo)	1.2	Single Administration

SAD phase will include a sentinel design in which two (2) participants at the given cohort dose be initially enrolled. If the dose can be well tolerated for 48 hours after full administration per site Principle Investigator's judgement, the remaining 6 participants will be enrolled to receive a single dose of MBS-COV at the same 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.

Part B (MAD Phase)

This is a randomized, double-blind, placebo-controlled study in approximately 20 healthy participants. Doses will be selected based on a comprehensive review of 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:

Table 3-2: MAD Phase Cohorts

Cohort		Number of Participants	MBS-COV Dose (mg/kg)	Dose
MAD Phase	B1	8 (MBS-COV) +2 (placebo)	0.6	Once daily for 7 days
	B2	8 (MBS-COV) +2 (placebo)	1.2	Once daily for 7 days

Study Visits:

- **Screening Visit** (SV: Up to 28 Days prior to Day 1): Consists of signing the ICF and study qualification based on evaluation of inclusion/exclusion criteria.
- **Treatment Visit 0** (T0: Day -1): All participants continuing to meet eligibility criteria will be enrolled into the study and confined to research clinic until Day 2 for cohort A1 to A3 (SAD phase) and Day 9 for cohort B1 to B2 (MAD phase).
- **Treatment Visit 1: Baseline Visit** (T1: Day 1)**:** The first assigned study treatment dose will be administered after completion of all study evaluations. Adverse events and changes in concomitant medications will be collected. Participants in Cohorts A1 to A3 will inhaled a single dose of MBS-COV or placebo through a portable nebulizer on Day 1. Participants in cohort B1 and B2 will receive doses of MBS-COV or placebo by through a portable nebulizer once daily for 7 consecutive days from Day 1 to Day 7.

Part A (SAD Phase)

  - **Treatment Visit 2** (T2: Day 2)
  - **Treatment Visit 3** (T3: Day 3)
  - **Treatment Visit 4** (T4: Day 4)
  - **Treatment Visit 5 (End of Treatment)** (T5: Day 7)

- **Follow-Up Visit 1（FU1: Day 14）**
- **Follow-Up Visit 2 (FU2: Day 28)**

Part B (MAD Phase)

- **Treatment Visit 2** (T2: Day 2)
- **Treatment Visit 3** (T3: Day 3)
- **Treatment Visit 4** (T4: Day 4)
- **Treatment Visit 5** (T5: Day 5)
- **Treatment Visit 6** (T6: Day 6)
- **Treatment Visit 7** (T7: Day 7)
- **Treatment Visit 8** (T8: Day 8)
- **Treatment Visit 8 (End of Treatment) (**T9: Day 9)

- **Follow-Up Visit 1** (FU1: Day 14)
- **Follow-Up Visit 2** (FU2: Day 28)

If any of the dose escalation stopping criteria have occurred in Part A or Part B, the SRC will make a final recommendation for dose escalation to the next cohort.

- **NOTE:** The dose escalation decision through the study will not be made until the following:

(1) All study participants in a given cohort have been enrolled,

(2) All such participants have completed Treatment Visit 5 (Day 7) (for SAD-Part A) and Treatment Visit 9 (Day 9) (for MAD-Part B) of the study or withdrawn from the study, whichever occurs first,

(3) The SRC will review the available safety data and recommend further dose escalation.

Additionally, dose escalation stopping criteria are defined per the below:

a. Death in any participant in which the cause of death is judged to be possibly, probably or definitely related to MBS-COV.

b. The occurrence in any participant of a severe local application site reaction (Grade 3 which doesn't resolve or recurs, or Grade 4) that is judged to be possibly, probably or definitely related to MBS-COV.

c. The occurrence in any participant of a SAE whose causal relationship to MBS-COV is judged to be probably, possibly, or definitely related to MBS-COV.

d. The occurrence, in two or more participants of Grade 3 AE or laboratory abnormalities, judged to be probably, possibly, or definitely related to MBS-COV.

e. The occurrence of two of the same AE or laboratory abnormality ≥ Grade 3 judged to be probably, possibly, or definitely related to receipt of MBS-COV

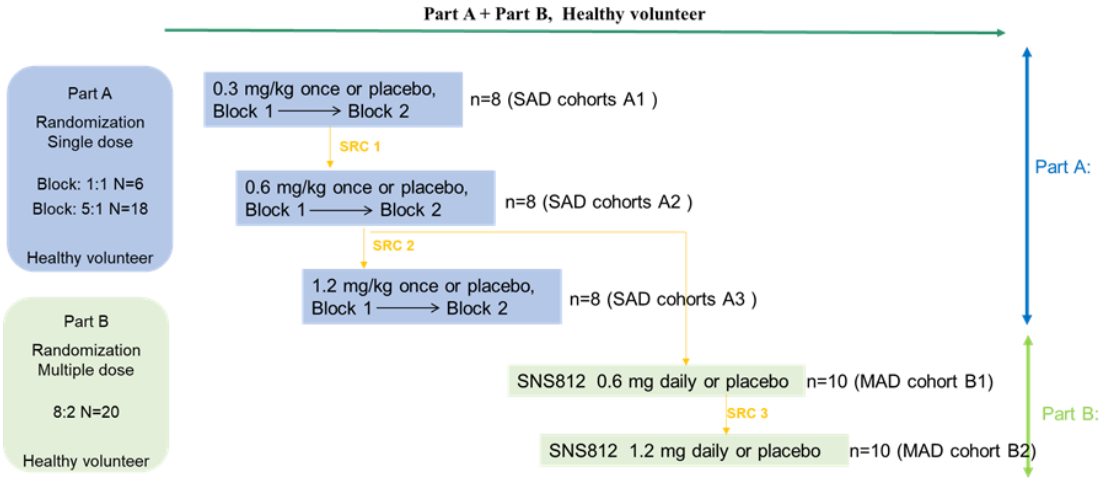
f. The occurrence, in one or more participants of Grade 4 AE or laboratory abnormalities, judged to be probably, possibly, or definitely related to receipt of MBS-COV.

g. Any pattern of significant symptoms, physical findings, or laboratory abnormalities that, although individually minor, collectively represent a safety concern in the opinion of the investigator and are judged by the SRC to be at least possibly related to MBS-COV.

h. PK exposure limits of mean AUC of 385.6 h*ng/mL or C_{max} of 141.8 ng/mL for one cohort, whichever comes first.(Single dose: AUC of 386.9 h*ng/mL or C_{max} of 91.7 ng/mL).

The SRC will review the PK data (if applicable) and safety trends of available information 7-day post treatment period of Cohort A1 and A2 (or if study stops prematurely due to safety reasons), to start part B of the study. The starting dose of Part B will be determined by SRC.

Figure 3-1: Dose Escalation Scheme



Blood Sample Collection for the PK study:

- SAD cohorts A1 to A3: For the single dose on day 1, blood samples will be collected before dosing, and afterwards at 5 min (± 1 min), 15 min (± 2 min),0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 4 h (± 5 min), 8 h (± 10 min), 10 h (± 10 min), 24 h (± 10 min) and 48 h (± 10 min) (Total 11 samples) after dosing.
- MAD cohort B1 and B2: Blood samples will be collected on Day 1 and Day 7 before dosing, and afterwards at 5 min (± 1 min), 15min (± 2 min), 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 4 h (± 5 min), 8 h (± 10 min), 10 h (± 10 min) on Day 1; and at 5 min (± 1 min), 15min (± 2 min), 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 4 h (± 5 min), 8 h (±

10 min), 10 h (± 10 min) , 24 h (± 10 min) and 48 h (± 10 min) after dosing on Day 7; and before dosing on Day 2 to Day 6 (Total 25 samples). The detailed study schedule and assessments in each visit are provided in Section 4 of the protocol.

Blood Sample Collection for the immunogenicity study:

- Blood Sample will be collected on Day 1 before dosing, Day 14 and Day 28 for SAD and MAD cohorts, and the analysis will be performed when analytic method is well-established.

3.2. STUDY CENTER

One study center in the United States (US).

3.3. STUDY POPULATION

The target population for this study will be healthy participants.

3.4. ELIGIBILITY CRITERIA

3.4.1. Inclusion Criteria

Participants will be eligible for enrollment in the study only if they meet ALL the following criteria at time of Screening:

1. Male or female adults who are between 18 and 55 years old (inclusive).
2. Body mass index (BMI) between 18.0 and 32.0 kg/m^2 (inclusive).
3. No serious or chronic underlying disease which would adversely affect the study conduct and data interpretation per the Investigator.
4. Female participants should have negative results in serum pregnancy test at screening and negative urine pregnancy test at admission (Day -1).
5. Participants with normal spirometry (FEV1 %: 80 % or greater) results at screening or day -1.
6. Both male and female participants and their partners of childbearing potential must agree to use two medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], or one of the following methods of birth control (intrauterine devices, tubal sterilization or vasectomy) or must practice complete abstinence from intercourse of reproductive potential from study entry to 3 months after the last day of treatment (excluding women who are not of childbearing potential and men who have been sterilized).

7. Participants should have normal (or abnormal but not clinically significant) laboratory results per the PI's judgement including the hematology, biochemistry, coagulation indices and urinalysis.
8. Participants should have a normal (or abnormal but not clinically significant) 12-lead ECG at screening and day -1 and chest X-ray at screening.
9. Participants should be willing to cooperate and able to participate in this study, comply with all protocol requirements, and sign an informed consent.
10. Current non-smokers and those who have not smoked within the last 3 months. This includes the use of cigarettes, e-cigarettes, and nicotine replacement products.
11. Nasopharyngeal or nasal swab sample of Participants collected for COVID-19 antigen rapid test at screening and qRT-PCR test on Day -1 should be negative.

3.4.2. Exclusion Criteria

Participants meeting ANY of the following criteria at time of Screening will be excluded from enrollment:

1. The participant has a known history of, or a positive test result for, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at screening.
2. As reported by the participant has severe cardiovascular disease, neurological disease, hematological disease, infectious disease, mental disorder, liver disease, gastrointestinal disease, lung disease, endocrine disease, immune disease or kidney disease, or has a history of the above diseases, or other symptoms known to interfere with the absorption, distribution, metabolism, or excretion of the medicine, or other conditions that the Investigator believes will increase the risk of the participant and might interfere with the study conduct and results interpretation.
3. The participant has history or presence of active lung disease (i.e., asthma, chronic obstructive pulmonary disease [COPD], pulmonary fibrosis, hemoptysis, bronchiectasis) or prior intubation due to respiratory failure conditions.
4. The participant has upper respiratory infection within the 3 months prior to the first dose of study drug.
5. Consumed more than 14 units of alcohol per week in the 6 months before screening (1 unit of alcohol = 360 mL of beer or 45 mL of spirits with 40% alcohol content or 150 mL of wine) or have taken alcohol products in the 48 hours prior to administration, or those who have a positive alcohol breath test result at screening and day -1.
6. Unwillingness to abstain from the consumption of any caffeine or alcohol-containing food or drinks that may influence the drug metabolism from 48 hours before administration.

7. History of drug abuse or a positive drug abuse (barbiturates, methamphetamine, benzodiazepines, morphine/opiates, phencyclidine (PCP), amphetamines, tetrahydrocannabinol (THC), methylenedioxymethamphetamine (MDMA), cocaine, methadone, and cotinine) test result at screening and day -1.
8. Female participants who are lactating.
9. Use of prescription or non-prescription drugs, including vaccine within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study drug.
10. The participant has received an experimental agent (vaccine, drug, biologic, device, blood product or medication) within 1 month prior to the first dose of study drug and will receive another experimental agent during the duration of this study.
11. The participant has a history of frequent nose bleeding.
12. Participants with known allergic reactions to the study drug or its excipients.
13. The participant has an acute sinusitis or history of chronic sinusitis, a history of active allergic rhinitis (AR), history of perennial allergic rhinitis (PAR), or current seasonal allergic rhinitis (SAR), or recent viral rhinitis within 2 weeks prior to administration.
14. The participant has Any nasopharyngeal abnormality that may have interfered with nasal absorption, distribution, or study-related evaluations of signs or symptoms (e.g., polyps, septal deviation).
15. Blood donation of more than 400 mL within 3 months before screening or more than 200 mL within 4 weeks before screening or plan to donate blood during study period.
16. Any other clinical condition that, in the Investigator's judgment, would potentially compromise study compliance or the ability to evaluate safety/efficacy.

4. STUDY SCHEDULE

4.1. OVERVIEW

The study Schedule of Assessments in presented in Table 4-1 (Part A) and Table 4-2 (Part B). See Section 7 for a detailed description of each protocol assessment and procedure.

The study is divided into three phases: Screening Phase, Treatment Phase, and Follow-Up Phase.

Table 4-1: Schedule of Assessments – Part A (SAD Phase)

Procedure/Assessments	Screening Phase	Treatment Phase							Follow-Up Phase	
		Inpatient Visit					Outpatient Visits			
Visit	SV	T0	T1 (Baseline)		T2	T3	T4	T5 (EOT/ET)	FU1	FU2[19]
			(Pre-Rx)	(Post-Rx)						
Day	Up to -28	Day -1	Day 1		Day 2	Day 3 (48 hours after dosing)	Day 4	Day 7	Day 14	Day 28
Window Period			Within 28 days of the Screening Visit		NA	NA	NA	±1	±1	±1
ASSESSMENTS										
Informed Consent [1]	X									
Eligibility Evaluation [2]	X	X								
Participant Demographics	X									
Medical History [3]	X	X	X							
Physical Examination	X		X	X[4]	X[4]	X[4]	X[4]	X[4]	X	
Height, Weight and BMI	X									
Vital Signs	X	X	X	X[5]	X	X	X	X	X	
12-lead ECG	X	X	X	X[6]	X	X	X	X	X	
Chest X-ray	X							X		
Spirometry assessments [7]	X	X		X						
Participant Confined to Research Clinic		X	X	X	X					
Participant Discharge from Research Clinic (if applicable) [8]						X				
Randomization			X							
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events				X	X	X	X	X	X	X
LABORATORY TESTS[9]:										
Hematology [10]	X	X			X	X		X	X	
Biochemistry [11]	X	X			X	X		X	X	
Coagulation Indices [12]	X	X			X	X		X	X	
Serum/Urine Pregnancy Test [13]	X	X						X	X	
Urinalysis [14]	X	X			X	X		X	X	

Procedure/Assessments	Screening Phase	Treatment Phase						Follow-Up Phase	
		Inpatient Visit				Outpatient Visits			
Visit	**SV**	**T0**	**T1 (Baseline)**		**T2**	**T3**	**T4**	**T5 (EOT/ET)**	**FU1**	**FU2[19]**
			(Pre-Rx)	(Post-Rx)						
Day	Up to -28	Day -1	Day 1		Day 2	Day 3 (48 hours after dosing)	Day 4	Day 7	Day 14	Day 28
Window Period			Within 28 days of the Screening Visit		NA	NA	NA	±1	±1	±1
Nasopharyngeal or nasal swab for COVID-19 [15]	X	X				X	X	X	X	X
Urine Drug and Alcohol Screening	X	X								
PK evaluations [16]			X	X	X	X				
ADA[17]			X						X	X
Screening for infectious diseases (HIV antibody; HbsAg; HCV antibody)	X									
INTERVENTION(s):										
MBS-COV Administration [18]			X							

[1] Informed consent must be obtained prior to participation in any protocol-related activities that are not part of routine care.
[2] Initial evaluation of participant eligibility will be performed by Investigator.
[3] Medical history and current therapies (medications and non-medications).
[4] Symptom-directed physical examination.
[5] Vital signs will include blood pressure, pulse, respiration rate, and temperature. On treatment visits will be conducted three times a day, within 120 minutes before administration, within 1 hour after administration, and 4-6 hours after administration, respectively. On other visits will be conducted once during the visit.
[6] 12-lead ECG on treatment visits will be conducted three times a day, within 120 minutes before administration, within 1 hour after administration, and 4-6 hours after administration, respectively. On other visits will be conducted once during the visit.
[7] Spirometry assessments will be started 5 minutes after the dosing with frequent spirometry measurements at 5 (± 1 min), 15 (± 1 min), 30 (± 5 min), 60 minutes (± 5 min). On other visits will be conducted once during the visit. If spirometry is completed within 7 days prior to dosing, this assessment does not need to be repeated on Day-1.
[8] Participants will be discharge from the clinic when all required assessments for T3 Day (3) are performed.
[9] If hematology, biochemistry, coagulation and urinalysis are completed within 7 days prior to dosing, this assessment does not need to be repeated on Day-1.
[10] Hematology
Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total and differential count, Absolute Neutrophil Count (ANC) and platelets.
[11] Biochemistry
Hepatic function indicators: total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, Lactate dehydrogenase (LDH), amylase and lipase

Renal function indicators: Serum creatinine, eGFR
Electrolytes: sodium, potassium, chloride, calcium and bicarbonate
Other: glucose (random), triglyceride (TG), cholesterol (total), Creatine kinase.

[12] Coagulation
Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB)

[13] Serum pregnancy test in screening visit (Will include FSH and estradiol levels at screening for post-menopausal women only) and EOT, and Urine pregnancy test in other visits.

[14] Urine samples will be tested for color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin, and urobilinogen.

[15] Nasopharyngeal or nasal swab sample will be collected for COVID-19 antigen rapid test at screening and qRT-PCR test on Day -1, Day 3, Day 4, Day 7, Day 14 and Day 28.

[16] PK timepoints: Cohorts A1 to A3: For the single dose on day 1, blood samples will be collected before dosing, and afterwards at 5 min (± 1 min), 15 min (± 2 min), 0.5h (± 5 min), 1h (± 5 min), 2h (± 5 min), 4h (± 5 min), 8h (± 10 min), 10 h (± 10 min), 24 h (± 10 min) and 48 h (± 10 min) after dosing.

[17] ADA timepoints: Blood samples will be collected on Day 1 before dosing, Day 14, and Day 28.

[18] IP administration: SAD cohorts A1-A3: Single MBS-COV treatment administration through a portable nebulizer (0.3 - 1.2 mg/kg).

[19] Adverse events and concomitant medications will be followed up on Day 28.

Table 4-2: Schedule of Assessments – Part B (MAD Phase)

Procedure/Assessments	Screening Phase	Treatment Phase						Follow-Up Phase	
		Inpatient Visits							
Visit	**SV**	**T0**	**T1 (Baseline)** (Pre-Rx)	**T1 (Baseline)** (Post-Rx)	T2-T7	**T8**	**T9(EOT/ET)**	**FU1**	**FU2[19]**
Day	Up to -28	Day -1	Day 1		Day 2-Day 7	Day 8	Day 9 (48 hours after last dosing)	Day 14	Day 28
Window Period			Within 28 days of the Screening Visit		NA	NA	±1	±1	±1
ASSESSMENTS									
Informed Consent [1]	X								
Eligibility Evaluation [2]	X	X							
Participant Demographics	X								
Medical History [3]	X	X	X						
Physical Examination	X		X	X[4]	X[4]	X[4]	X[4]	X	
Height, Weight and BMI	X								
Vital Signs	X	X	X	X[5]	X[5]	X	X	X	
12-lead ECG	X	X	X	X[6]	X[6]	X	X	X	
Chest X-ray	X						X		
Spirometry assessments [7]	X	X		X	X				
Participant Confined to Research Clinic		X	X	X	X	X			
Participant Discharge from research clinic (if applicable) [8]							X		
Randomization			X						
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events				X	X	X	X	X	X
LABAROTORY ASSESSMENTS[9]									
Hematology [10]	X	X			X	X	X	X	
Biochemistry [11]	X	X			X	X	X	X	
Coagulation Indices [12]	X	X			X	X	X	X	
Serum/Urine Pregnancy Test [13]	X	X					X	X	

Procedure/Assessments	Screening Phase	Treatment Phase						Follow-Up Phase	
		Inpatient Visits							
Visit	**SV**	**T0**	**T1 (Baseline)** (Pre-Rx)	**T1 (Baseline)** (Post-Rx)	T2-T7	**T8**	**T9(EOT/ET)**	**FU1**	**FU2[19]**
Day	Up to -28	Day -1	Day 1		Day 2-Day 7	Day 8	Day 9 (48 hours after last dosing)	Day 14	Day 28
Window Period			Within 28 days of the Screening Visit		NA	NA	±1	±1	±1
Urinalysis [14]	X	X			X	X	X	X	
Nasopharyngeal or Nasal Swab for COVID-19 [15]	X	X					X	X	X
Urine Drug and Alcohol Screening	X	X							
PK evaluations [16]			X	X	X	X	X		
ADA [17]			X					X	X
Screening for infectious diseases (HIV antibody; HbsAg; HCV antibody)	X								
INTERVENTON(s)									
MBS-COV Administration [18]			X		X				

[1] Informed consent must be obtained prior to participation in any protocol-related activities that are not part of routine care.
[2] Initial evaluation of participant eligibility will be performed by Investigator.
[3] Medical history and current therapies (medications and non-medications).
[4] Symptom-directed physical examination.
[5] Vital signs will include blood pressure, pulse, respiration rate, and temperature. On treatment visits will be conducted three times a day, within 120 minutes before administration, within 1 hour after administration, and 4-6 hours after administration, respectively. On other visits will be conducted once during the visit.
[6] 12-lead ECG on treatment visits will be conducted three times a day, within 120 minutes before administration, within 1 hour after administration, and 4-6 hours after administration, respectively. On other visits will be conducted once during the visit.
[7] Spirometry assessments will be started 5 minutes after the dosing with frequent spirometry measurements at 5 (± 1 min), 15 (± 1 min), 30 (± 5 min) 60 (± 5 min) minutes. On other visits will be conducted once during the visit.
[8] Participant will be discharge from the clinic when all required assessments for V9 are performed.
[9] If hematology, biochemistry, coagulation and urinalysis are completed within 7 days prior to dosing, this assessment does not need to be repeated on Day-1.
[10] Hematology
Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total and differential count, Absolute Neutrophil Count (ANC) and platelets.
[11] Biochemistry

Hepatic function indicators: total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin Lactate dehydrogenase (LDH), amylase and lipase

Renal function indicators: Serum creatinine, eGFR

Electrolytes: sodium, potassium, chloride, calcium and bicarbonate

Other: glucose (random) , triglyceride (TG), cholesterol (total), Creatine kinase.

[12] Coagulation

Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB)

[13] Serum pregnancy test in screening visit (Will include FSH and estradiol levels at screening for post-menopausal women only) and EOT, and Urine pregnancy test in other visits.

[14] Urine samples will be tested for color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin, and urobilinogen.

[15] Nasopharyngeal or nasal swab sample will be collected for COVID-19 antigen rapid test at screening and qRT-PCR test on Day -1, Day 9, Day 14 and Day 28.

[16] PK timepoints: Cohorts B1 to B2: Blood samples will be collected on Day 1 and Day 7 before dosing, and afterwards at 5 min (± 1 min), 15min (± 2 min), 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 4 h (± 5 min), 8 h (± 10 min), 10 h (± 10 min) on Day 1; and at 5 min (± 1 min), 15min (± 2 min), 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 4 h (± 5 min), 8 h (± 10 min), 10 h (± 10 min), 24 h (± 10 min) and 48 h (± 10 min) after dosing on Day 7; and before dosing on Day 2 to Day 6 (Total 25 samples).

[17] ADA timepoints: Blood samples will be collected on Day 1 before dosing, Day 14, and Day 28.

[18] IP administration: MAD cohorts B1-B2: MBS-COV treatment administration through a portable mesh nebulizer for 7 consecutive days, once daily, according to the cohort dosing schedule

[19] Adverse events and concomitant medications will be followed up on Day 28.

4.2. PART A

4.2.1. Part A (SAD) - Screening Visit (SV: Up to 28 Days prior to Day 1):

The participant will sign and date the ICF, and screening visit procedures of Part A of the study are per below:

- Informed consent will be obtained prior to any study-related procedures
- Eligibility assessment per the inclusion and exclusion criteria
- Participant demographics
- Medical history
- Vital signs
- Height, Weight, BMI
- Physical examination
- 12-lead electrocardiogram (12-lead ECG)
- Chest X-ray
- List concomitant medications
- Spirometry assessment
- Laboratory assessments (hematology, chemistry, coagulation and urine analysis, urine drug screening and alcohol screen)
- Screening for infectious diseases (HIV antibody; HbsAg antigen; HCV antibody positive)
- Serum pregnancy test
- Nasopharyngeal or nasal swab for COVID-19

If spirometry, hematology, chemistry, coagulation, and urine analysis, are completed within 7 days prior to dosing, this assessment does not need to be repeated on Day-1.

4.2.2. Part A (SAD) - Treatment Visit 0 (T0: Day -1)

If continued to be eligible for the study at Treatment Visit 0 per below, the participant will proceed to be enrolled into Part A (SAD) of the study in next visit.

- Assessment of continued eligibility
- Medical history
- Vital signs
- 12-lead ECG

- List concomitant medications
- Spirometry assessment
- Participant confined to research clinic
- Laboratory assessments (hematology, chemistry, coagulation and urine analysis, urine drug screening and alcohol screen)
- Urine pregnancy test
- Nasopharyngeal or nasal swab for COVID-19

4.2.3. Part A (SAD) - Treatment Visit 1: Baseline Visit (T1: Day 1)

The first assigned study treatment dose will be administered after completion of all study evaluations. Adverse events and changes in concomitant medications will be collected. Participants in Cohorts A1 to A3 will be inhaled a single dose of MBS-COV or placebo through a portable nebulizer on Day 1.

The following assessments will be performed:

- Medical history (pre dose)
- Vital signs (pre and post dose) (Vital signs will include blood pressure, pulse, respiration rate, and temperature. On treatment visits will be conducted three times a day, within 120 minutes before administration, within 1 hour after administration, and 4-6 hours after administration, respectively.)
- Randomization (pre dose)
- Physical examination (pre and post dose)
- 12-lead ECG (pre and post dose) (12-lead ECG on treatment visits will be conducted three times a day, within 120 minutes before administration, within 1 hour after administration, and 4-6 hours after administration, respectively.)
- List concomitant medications
- PK timepoints: Cohorts A1 to A3: For the single dose on day 1, blood samples will be collected before dosing, and afterwards at 5 min (± 1 min), 15 min (± 2 min), 0.5 h (± 2 min), 1 h (± 5 min), 2 h (± 5 min), 4 h (± 5 min), 8 h (± 10 min), 10 h (± 10 min) after dosing.
- ADA timepoints: Blood samples will be collected on Day 1 before dosing
- Spirometry Assessment (Spirometry assessments will be started 5 minutes after the dosing with frequent spirometry measurements at 5 (± 1 min), 15 (± 1 min), 30 (± 5 min), 60 minutes (± 5 min).)

- Adverse events evaluation after first dose
- Participants will be confined till 24 hours pharmacokinetic samples are obtained following study drug administration.

4.2.4. Part A (SAD) – Treatment Visit 2 to Treatment Visit 5/End of Treatment (T2: Day 2 to T5: Day 7)

The following assessments will be performed (refer to the schedule of events Table 4-1)

- Vital signs
- Physical examination, including dermatologic examination
- 12-lead ECG
- List concomitant medications
- Laboratory assessments (hematology, chemistry, coagulation and urine analysis) (T2, T3, and T5 only)
- Chest X-ray (T5 only)
- PK timepoints: Cohorts A1 to A3: For the single dose on day 1, blood samples will be collected at 24 h (± 10 min) and 48h (± 10 min) after dosing.
- Serum pregnancy test only on T5 (EOT)
- Adverse events evaluation
- Nasopharyngeal or nasal swab for COVID-19 (T3, T4 and T5)
- Participants will be discharged from the clinic on Day 3. if applicable.

4.2.5. Part A (SAD) – Follow-Up Visit 1 (FU1: Day 14)

A Follow-Up visit will be conducted to evaluate safety and study evaluations. Adverse events and changes in concomitant medications will be collected. The following assessments will be performed:

- Vital signs
- Physical examination
- 12-lead ECG
- List concomitant medications
- Laboratory assessments (hematology, chemistry, coagulation, and urine analysis)
- ADA timepoints: Cohorts A1 to A3: For the single dose on day 1, blood samples will be collected at day 14 after dosing.

- Urine pregnancy test
- Adverse events evaluation
- Nasopharyngeal or nasal swab for COVID-19

4.2.6. Part A (SAD) – Follow-Up Visit 2 (FU2: Day 28)

The following assessments will be performed:

- ADA sampling
- Nasopharyngeal or nasal swab for COVID-19
- Adverse events evaluation
- Changes in concomitant medications

4.3. PART B STUDY VISITS

4.3.1. Part B (MAD) - Screening Visit (SV: Up to 28 Days prior to Day 1)

The participant will sign and date the ICF, and screening visit procedures of Part B of the study are per below:

- Informed consent will be obtained prior to any study-related procedures
- Eligibility assessment per the inclusion and exclusion criteria
- Participant demographics
- Medical history
- Vital signs
- Height, Weight, and BMI
- Physical examination
- 12-lead ECG
- Chest X-ray
- List concomitant medications
- Spirometry assessment
- Laboratory assessments (hematology, chemistry, Coagulation, and urine analysis), Urine Drug Screening, and alcohol screen, Screening for infectious diseases (HIV antibody; HbsAg; HCV antibody)
- Serum pregnancy test
- Nasopharyngeal or nasal swab for COVID-19

These assessments must be conducted within 28 days of the First Treatment Visit (T1). Screening information will be fully documented in the participant's medical records (i.e., source documents).

For consented participants who do not meet eligibility criteria, a Screen Failure Case Report Form (CRF) will be completed. The Screen Failure CRF will contain the following details: the participant identification number, the date of ICF signature, demographic information, and the reason for screen failure. No additional information will be required for participants who fail screening.

For consented participants who meet eligibility criteria, all required screening information will be transcribed onto the appropriate page of the CRF.

4.3.2. Part B (MAD) - Treatment Visit 0 (T0: Day -1)

Participants who meet the eligibility criteria will have completed the following evaluations and assessments at T0:

- Assessment of continued eligibility
- Review of any changes in medical and medical history
- List concomitant medications
- Vital signs
- Spirometry assessment
- Participant confined to research clinic
- Laboratory assessments (hematology, chemistry, coagulation, and urine analysis), Urine Drug Screening, and alcohol screen
- Urine pregnancy test
- 12-lead ECG
- Nasopharyngeal or nasal swab for COVID-19

If spirometry, hematology, chemistry, coagulation, and urine analysis, are completed within 7 days prior to dosing, this assessment does not need to be repeated on Day-1.

4.3.3. Part B (MAD) - Treatment Visit 1: Baseline Visit (T1: Day 1):

At T1, participants will be enrolled to receive the assigned study treatment which will be administered daily at Treatment Visits 1 to 7 by a qualified medical professional at clinic.

- Review of any changes in medical and medical history (pre dose)
- Vital signs (pre and post dose) (Vital signs will include blood pressure, pulse, respiration rate, and temperature. On treatment visits will be conducted three times a day, within 120

minutes before administration, within 1 hour after administration, and 4-6 hours after administration, respectively.)

- Physical examination (pre and post dose)
- Randomization (pre dose)
- 12-lead ECG (12-lead ECG on treatment visits will be conducted three times a day, within 120 minutes before administration, within 1 hour after administration, and 4-6 hours after administration, respectively.)
- PK timepoints: Blood samples will be collected on Day 1 before dosing, and afterwards at 5 min (± 1 min), 15min (± 2 min), 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 4 h (± 5 min), 8 h (± 10 min), 10 h (± 10 min) after dosing.
- ADA timepoints: Blood samples will be collected on Day 1 before dosing
- Spirometry Assessment (Spirometry assessments will be started 5 minutes after the dosing with frequent spirometry measurements at 5 (± 1 min), 15 (± 1 min), 30 (± 5 min), 60 minutes (± 5 min).)
- List concomitant medications
- Adverse events evaluation after first dose
- Study drug administration

IP administration: MBS-COV treatment administration through a portable nebulizer (0.6 and 1.2 mg/kg) for 7 consecutive days, once daily, according to the cohort dosing schedule

In part B participants will be randomized 8:2 to MBS-COV or placebo in the assigned cohort.

4.3.4. Part B (MAD) – Treatment Visit 2 to Treatment Visit 7 (T2: Day 2 to T7: Day 7)

During Treatment Visit 2 to Treatment Visit 7, the following assessments will be performed per the study schedule of assessments Table 4-2.

- Vital signs (Vital signs will include blood pressure, pulse, respiration rate, and temperature. On treatment visits will be conducted three times a day, within 120 minutes before administration, within 1 hour after administration, and 4-6 hours after administration, respectively.)
- Physical examination
- Laboratory assessments (hematology, chemistry, coagulation, and urine analysis)
- PK timepoints: Blood samples will be collected before dosing on Day 2 to Day 6, and on Day 7 before dosing, and afterwards at 5 min (± 1 min), 15min (± 2 min), 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 4 h (± 5 min), 8 h (± 10 min), and 10 h (± 10 min) after dosing on Day 7

- 12-lead ECG (12-lead ECG on treatment visits will be conducted three times a day, within 120 minutes before administration, within 1 hour after administration, and 4-6 hours after administration, respectively.)
- Study drug administration
- Spirometry Assessment (Spirometry assessments will be started 5 minutes after the dosing with frequent spirometry measurements at 5 (± 1 min), 15 (± 1 min), 30 (± 5 min), 60 (± 5 min) minutes).
- List concomitant medications
- Adverse events evaluation

Participants will be discharged from the clinic on Day 9 if applicable.

4.3.5. Part B (MAD) - Treatment Visit 8 (T8: Day 8)

The following assessments will be performed:

- Vital signs
- Physical examination
- 12-lead ECG
- Laboratory assessments (hematology, chemistry, coagulation and urine analysis)
- PK timepoints: Blood samples will be collected on Day 8
- List concomitant medications
- Adverse events evaluation

4.3.6. Part B (MAD) - Treatment Visit 9 (End of Treatment) (T9: Day 9)

The following assessments will be performed:

- Vital signs
- Physical examination
- 12-lead ECG
- Chest X-ray
- Laboratory assessments (hematology, chemistry, coagulation and urine analysis)
- PK timepoints: Blood samples will be collected on Day 9
- Serum pregnancy test
- Nasopharyngeal or nasal swab for COVID-19

- List concomitant medications
- Adverse events evaluation
- Participants will be discharged from the clinic on Day 9. if applicable.

4.3.7. Part B (MAD) - Follow-Up Visit 1 (FU1: Day 14)

A Follow-up visit will be performed 1 week (FU1) after last day of study drug administration. To ensure the safety of participants and site staff. The following assessments will be performed:

- Vital signs
- Physical examination
- 12-lead ECG
- Nasopharyngeal or nasal swab for COVID-19
- Laboratory assessments (hematology, chemistry, coagulation and urine analysis)
- ADA timepoints: Blood samples will be collected on Day 14
- Urine pregnancy test
- List concomitant medications
- Adverse events evaluation

4.3.8. Part B (MAD) - Follow-Up Visit 2 (FU2: Day 28)

The following assessments will be performed:

- ADA sampling
- Nasopharyngeal or nasal swab for COVID-19
- Adverse events evaluation
- Changes in concomitant medications

4.4. UNSCHEDULED VISITS

In the event that the participant will return to clinic at a time other than a regularly scheduled study visit, the visit will be regarded as an unscheduled visit. This includes when participants require rescue therapy or need interim care due to chronic illness. Assessments at unscheduled visits are at the discretion of the Investigator. All pertinent findings, including adverse events or changes in medications, will be noted in the CRF.

4.5. MISSED VISITS

If a participant misses a visit, the site is to make every effort to have the participant return as soon as possible to make up the visit.

5. PARTICIPANT COMPLETION, WITHDRAWAL AND CRITERIA FOR STOPPING THE STUDY

5.1. PARTICIPANT COMPLETION

5.1.1. Definition of Study Treatment Completion

5.1.1.1. End of Treatment (EOT) Completion

A participant is considered to have completed the treatment phase if all scheduled treatment visits have been completed.

5.1.1.2. End of Follow-Up (EOFU) Completion

A participant is considered to have completed the follow-up phase if all scheduled follow-up visits have been completed.

5.2. PARTICIPANT WITHDRAWAL

At any point during the study all participants have the right to withdraw without prejudice to future care. Documentation to whether or not each participant completed the clinical study will be recorded. If study treatment is discontinued for any participant, the reason(s) will be documented.

5.2.1. Participant Discontinuation

The Investigator can discontinue a participant at any time if in their clinical judgment considers to be medically necessary. Investigators considering discontinuing study treatment should contact the medical monitor prior to such discontinuation. Participants who have study treatment discontinued will continue to be followed, per protocol, whenever possible. Participants who have study treatment discontinued due to a serious adverse event will be followed until resolution or stabilization of the event as described in Section 9.4.1 (SAE Follow-Up).

In addition, participants will be discontinued from the study in the following conditions:

- Withdrawal of consent.
- The participant has an AE and is unsuitable for the study as judged by the Investigator.
- The participant experiences events which significantly affect safety, tolerability, or PK profile of the drug, and is unsuitable for the study as judged by the Investigator.
- Participants have poor compliance or major protocol deviations occur is unsuitable for the study as judged by the investigator.
- The Investigator no longer believes participation is in the best interest of the participant.

5.2.2. Data Collected from Withdrawn Participants

In the case of early termination, assessments listed in Section 4.2.4 and Section 4.3.6 will be completed when possible.

Every attempt should be made to collect follow-up information. The reason for withdrawal from the study will be recorded in the source documents and on the appropriate page of the CRF.

Before a participant is identified as lost-to-follow up, the site should make all reasonable efforts to contact the participant. These attempts must be documented and should include at a minimum one phone call and one certified letter.

In the event that a participant is withdrawn from the study at any time due to an AE or SAE, the procedures stated in Section 9.2 (AE) or Section 9.4 (SAE) must be followed.

5.3. STUDY STOPPING CRITERIA

Upon occurrence of any of the following events, data will be reviewed by the Medical Monitor and the Lead Principal Investigator.

1. A significant unexpected AE occurs during the study, and the Investigator considers that the study should be terminated.
2. The study shall be terminated due to major violations of the clinical study protocol, GCP, or relevant regulations during the study.
3. The Sponsor requests termination under the premise of fully protecting the rights and safety of the participants (for financial reasons, management reasons, etc.).
4. The regulatory authority or Ethics Committee elects to terminate the study for certain reason.

In case the above listed event(s) occurred, participant accrual will be suspended pending further review and the FDA and other global regulatory authority will be notified. The study will be stopped if any of these stopping criteria are met unless, after reviewing the safety events of interest, the medical monitor and Sponsor, agree to allow the study to proceed. The FDA and other global regulatory authority will be consulted for any protocol amendment before restarting the study if a stopping rule is met.

6. STUDY TREATMENT

6.1. MBS-COV

The investigational product (IP) in this study is MBS-COV. MBS-COV is a sterile, excipient-free lyophilized powder with 50 mg of siRNA in a single dose 2-mL vial, to be reconstituted with normal saline before use for inhalation only at a to-be-determined dose level in milligram/kilogram per day, once daily, for 1 day or 7 consecutive days during this study. MBS-COV drug substance were manufactured at CCI . The study drug is only formulated with water for injection (WFI), then sterile filtration and lyophilization.

To administer the IP in all cohorts, MBS-COV powder is reconstituted with normal saline (0.9% Sodium Choloride Injection) before use and administered through a portable nebulizer, Vibrating mesh nebulizer Air Pro 3, for single dose groups and multi-dose groups.

6.1.1. Packaging and Labeling

Study drug will be prepared, packaged, and labeled by CCI , and will be shipped by sponsor-designated CRO.

Study treatment will be labeled, according to the regulatory guidelines, as an investigational product to ensure that it will not be used outside of the clinical investigation. The Sponsor, protocol number, expiry date and time, and any additional relevant information will appear on the pack label.

Example study treatment labels for both Part A and Part B is presented in Figure 6-1 and Figure 6-2.

Figure 6-1: Example Part A and Part B Study Treatment Vial Label

MBS-COV (SNS812) Powder For Inhalation Solution, 50 mg/vial

Batch No.：CT-22E002

Manufacturing Date：07-Jun-2022

Protocol No.：SNS812CLCT01

IP No.：

Caution: New Drug – Limited by Federal (or United States) law to investigational use

Figure 6-2: Box label for Clinical Study Treatment

【Product Name】：MBS-COV (SNS812) Powder For Inhalation Solution
【Batch Number】：CT-22E002
【Manufacturing Date】：07-Jun-2022
【Strength】：50 mg
【Shelf Life】：Tentative 24 months
【Packaging Quantity】：16 vials / Carton
【Storage】：Store at 2℃ to 8℃, protect from light
【Sponsor】：Oneness Biotech Co., Ltd
【Protocol No.】：SNS812CLCT01
Caution: New Drug – Limited by Federal (or United States) law to investigational use

【Product Name】：MBS-COV (SNS812) Powder For Inhalation Solution
【Package Quantity】：288 vials / Carton

6.1.2. Storage and Handling

All study treatment vials, MBS-COV and placebo must be stored in a secure area (e.g., a locked cabinet), protected from light, and be stored at refrigerated condition 2-8℃. Access to study treatments will be restricted to authorized personnel only.

The investigator must maintain an accurate record of the shipment, storage, and dispensing of the study drug in a drug accountability log. An accurate record including the date and amount of study drug dispensed to each participant must be available for inspection at any time. A study CRA assigned to monitor the investigational site will review these documents once study drug has been received by the investigational site. Study drug will be accounted for on an ongoing basis during the study.

6.1.3. Study Treatment Administration

Detailed guidelines for dose of formulation, administration technique and administration direction can be found in the study pharmacy manual.

All participants, after signing the Informed Consent Form (ICF), will be assessed during the screening phase. Eligible participants who have completed the screening phase will proceed with treatment phase of the study. Based on the phase of the study and randomization/Enrolment, study pharmacist will prepare the study drug for each participant and participants will be dosed individually at the pharmacy (or) designated space in the study site. Please refer to the study pharmacy manual for preparation of study drug prior to administration to each participant.

6.1.4. Study Treatment Dispensation

In both part of the study, the participants will be enrolled /randomized using a web-based randomization system (IWRS) and each participant enrolled into the study will receive assigned kit number including vials to be used via IWRS per the study enrolment/randomization scheme.

6.1.5. Study Treatment Accountability

Study treatments must be used in accordance with this protocol and only under the direction of the responsible investigator. The investigational site must maintain complete and accurate records showing receipt and disposition of all study treatments, including master records listing the date of receipt, the number of the kits received, and a dispensing record which includes each quantity dispensed, identification of the staff member to whom dispensed, the date of dispensing, the intended study participant number, and the identification of the preparer. All used and unused study kits will be retained by the investigational site until study treatment accountability can be confirmed by study CRA during the monitoring visits. Instructions will be provided by Sponsor regarding final disposition of all study drug in compliance with applicable regulations.

A study treatment accountability log will be provided to the site for use by the Investigator to maintain current and accurate inventory records (batch, expiry, and quantity) covering the receipt, dispensing and the return/destruction of all the study treatments.

At the conclusion of the study, the Investigator must agree to return or destroy all study materials as instructed by the Sponsor.

6.2. CONCOMITANT MEDICATIONS

Unless medication is necessary for safety reasons and approved by the Sponsor and the Investigator, participants must abstain from taking any prescription or non-prescription drugs, within 14 days or 5 times the half-life (whichever is longer) prior to the first dose of IP until completion of the study.

During the entire study period, participants must adhere to the following prohibitions:

- Able to abstain from the use of nicotine/tobacco containing products during the study.
- Able to abstain from the consumption of alcohol and any alcohol-containing products from 48 hours before dosing to the end of the study.
- Able to abstain from the consumption of coffee and any caffeine-containing products from 48 hours before dosing to the end of study.

7. DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

7.1. INFORMED CONSENT

A written informed consent will be obtained for this study by the Investigator or designee from all participants prior to performance of any protocol-specific procedure. This study will be conducted in accordance with the provisions of the Declaration of Helsinki.

The Investigator must comply with applicable regulatory requirements and must adhere to the Good Clinical Practice (GCP) in the process of obtaining and documenting the informed consent. The Investigator, or designee, must also inform participants of all pertinent aspects of the study. Before written informed consent is obtained from the participant, the Investigator or a person designated by the Investigator, must provide the participant enough time and opportunity to inquire about the details of the study and to decide whether or not to participate in the study. All questions addressed by the participant about the study must be answered to the satisfaction of the participant. Prior to the participant's participation in the study, the written informed consent must be signed and personally dated by the participant and by the person who conducted the informed consent discussion. Authorization for release of protected health information must also be obtained, as per local policies.

7.2. ASSESSMENT OF ELIGIBILITY

The Investigator must assess participant' continued eligibility for the study as per the Inclusion and Exclusion criteria, during the Screening Phase. The eligibility criteria are described in Section 3.4.1 (Inclusion Criteria) and Section 3.4.2 (Exclusion Criteria). In the event that the participant is not suitable or eligible for the study, the participant will be considered "screen failure".

7.2.1. Re-screening

A participant who signed a consent form but did not meet the inclusion/exclusion criteria is classified as a screen failure.

Note: If a participant initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the participant will be re-consented and assigned a new unique identification number at the time of re-screening. Participants who fail their first screening attempt may be re-screened a maximum of once and may be enrolled if they are found to meet all inclusion and no exclusion criteria when re-screened.

For consented participants who do not meet eligibility criteria, a Screen Failure Case Report Form (CRF) will be completed. The Screen Failure CRF will contain the following details: the participant identification number, the date of ICF signature, demographic information (see

Section 7.3), and the reason for screen failure. No additional information will be required for participants who fail screening.

7.3. DEMOGRAPHIC INFORMATION

In this study the demographic information will include:

- Dates of ICF signature
- Date of birth
- Gender
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, or Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, or Unknown)
- Use of tobacco or nicotine replacement products and e-cigarettes

7.4. MEDICAL HISTORY

A medical history will be recorded during the Screening Phase 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 and not as AEs. Aside from being used to determine participant eligibility, this information will permit the Investigator to record the nature, duration, and severity of any ongoing baseline medical conditions prior to the participant's receiving investigational product treatment.

For each relevant history, the following will be documented:

- Disease/disorder/condition
- Date of diagnosis
- History status (resolved or ongoing).

7.5. 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

Each abnormality will be recorded and the Investigator will record an assessment of its clinical significance.

7.6. VITAL SIGNS, HEIGHT AND WEIGHT

The following vital signs will be collected:

- Systolic and Diastolic Blood Pressure
- Pulse
- Respiratory Rate
- Oral Temperature

Blood pressure and pulse will be obtained in the supine position after participant has been resting for 5 minutes.

In addition, the following will be recorded:

- Height (Only performed at Screening visit)
- Weight
- Body Mass Index

7.7. CONCOMITANT MEDICATION

All medications and therapies administered or taken by the participant beginning 14 days prior to Screening Visit and throughout the study will be recorded in the source documents and on the appropriate page of the Case Report Form (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).
    - **Note:** *Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.*
- Route of dosing
- Indication for use
- The start date
- The stop date (if medication/therapy is not ongoing).

7.8. CLINICAL LABORATORY ASSESSMENTS

All laboratory assessments will be reviewed by the Investigator. If clinically significant findings, as determined by the Investigator, are recorded for a particular symptom, sign or abnormal measurement, that measurement will be repeated at medically appropriate intervals until the value returns to an acceptable range, a specific diagnosis is established, or the condition is otherwise explained.

Table 7-1: Lab Parameters

CBC Parameters	Biochemistry Parameters	Urinalysis
Hemoglobin (g/dL) Hematocrit (%) RBC/Erythrocytes (10^12/L) WBC/Leukocytes (10^6/L) Absolute Neutrophil Count (10^6/L) Platelets (10^9/L) Differential WBC: – Neutrophils (%) – Lymphocytes (%) – Monocytes (%) – Eosinophils (%) – Basophils (%)	**Liver Function Tests** 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) **Renal Function Tests** Serum creatinine (mg/dL) eGFR(ml/min/1.73 m^2) **Electrolytes** Sodium (mEq/L) Potassium (mEq/L) Chloride (mEq/L) Calcium (mg/dL) Bicarbonate (mEq/L) **Other:** Glucose, Random (mg/dL) Creatine kinase (U/L) Triglyceride (TG) (mg/dL) Total Cholesteriol (TC) (mg/dL) **Coagulation Parameters** Prothrombin time (PT) Activated partial thromboplastin time (APTT) Thrombin time (TT) Fibrinogen (FIB)	pH Specimen Appearance Color Specific Gravity Ketones Bilirubin Occult Blood Glucose Protein Nitrite Urobilinogen (mg/dL) Leukocyte Esterase
Miscellaneous		
Serum pregnancy test Urine pregnancy test (for female participants of childbearing potential) Drug in Urine Alcohol breath test Chest X-ray PK Evaluation ADA COVID-19 antigen rapid test at screening and qRT-PCR test		
Serology		
HBs Ag, HCV Ab and HCV RNA (if required), HIV Ab		

7.9. 12-LEAD ELECTROCARDIOGRAM

12-Lead ECG will be performed per the site standard procedures. The following parameters will be recorded (as part of the participant's medical record) and recorded on the appropriate page of

the CRF: ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec). Additionally, the Investigator will record the overall results of the 12-lead ECG reading as either normal or abnormal, and if abnormal, as either "not clinically significant" or "clinically significant." If abnormalities are observed, each will be recorded. Each treatment-emergent abnormality that is clinically significant will be recorded as an AE. Each 12-lead ECG should be signed by a physician. Clinically significant abnormal 12-lead ECG's may be repeated at the discretion of the Investigator.

7.10. NASOPHARYNGEAL SWAB OR NASAL SWAB FOR COVID-19

Nasopharyngeal or nasal swab sample will be collected for COVID-19 antigen rapid test at screening and qRT-PCR test according to Table 4-1 and Table 4-2. The participant will be followed, and samples will be collected for the entire duration of the study.

7.11. SPIROMETRY ASSESSMENT

It is to be used as a validation method to ensure participants don't have a former yet undiagnosed respiratory disease and to validate the presence of abnormal Forced Expiratory Volume1(FEV1) values.

Spirometry will evaluate the respiratory functions of acute bronchospasm. Spirometric parameter including FEV1% (the percent of predicted FEV1), FEV1/FVC, and peak expiratory flow (PEF).

Extra spirometry assessments may be repeated at the discretion of the investigator.

7.12. RANDOMIZATION

Healthy participants who are eligible to participate in the study will be randomized to one of the treatment groups via IWRS in assigned cohort (Interactive Web Based Randomization System) prior to IP administration.

8. STATISTICAL CONSIDERATIONS

This section presents general information about statistical considerations and concepts such as randomization, sample size, and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions will be included in a separate document; i.e., the Statistical Analysis Plan (SAP).

8.1. COHORTS/TREATMENT GROUPS

Refer to Table 3-1, and Table 3-2 for description of cohorts/treatment groups.

8.2. STUDY ENDPOINTS/ OUTCOME MEASURES

Refer to Section for list of study endpoints/outcome measures.

8.3. SAMPLE SIZE DETERMINATION AND RATIONALE

The sample size of at least 44 participants (24 healthy participants in part A and 20 healthy participants in part B) will be used in this study. This sample size is selected based on clinical judgment and not based on statistical power calculation; it is deemed adequate to provide clinically meaningful descriptive results consistent with study objectives.

8.4. RANDOMIZATION

In Part A (SAD Phase), 24 participants (8 per group) will be randomized in a 6:2 ratio (MBS-COV: placebo). In Part B (MAD Phase), a total of 20 participants (10 per group) will be randomized in a 8:2 ratio (MBS-COV: placebo)

An individual, independent of the clinical study team, will develop the randomization schedules. The actual randomization assignment will be made through a web based system. Participants who have provided written informed consent and have met all the inclusion criteria and none of the exclusion criteria will be randomized to one of the treatment groups.

8.5. BLINDING AND PREVENTION OF BIAS

8.6. INTERIM ANALYSIS

There is no efficacy interim analysis planned for this study; however, the safety data from all participants of each completed cohort will be reviewed by the SRC prior to enrolment of further participants or dose escalation.

8.7. GENERAL STATISTICAL CONSIDERATIONS

All collected study data will be presented in participant data listings and/or will be summarized. Statistical analyses will be performed using SAS® for Windows, version 9.4 or later.

A Statistical Analysis Plan (SAP) will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the efficacy and safety data from this study.

8.7.1. Statistical Analysis Populations

8.7.1.1. 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.

8.7.1.2. Safety 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.

8.7.1.3. PK concentration analysis set (PKCS)

PKCS includes all randomized participants who receive at least one dose of the study drug and have at least one plasma concentration. The PKCS will be used for PK concentration analysis.

8.7.1.4. PK parameters 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.

8.7.1.5. Immunogenicity Set (IS)

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.

8.7.2. Missing Data

All efforts will be made to minimize the amount of missing data for the study. The methods of handling missing data will be detailed in the SAP.

8.7.3. Statistical Methods

All safety analyses will be conducted using the Safety population.

For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented by treatment group. For categorical variables both frequencies and percentages will be presented by treatment group.

8.7.4. Participant Disposition

The disposition of all participants who signed an ICF will be provided. The numbers of participants screened, randomized (if applicable), received treatment, completed, and discontinued during the study, as well as the reasons for discontinuation will be summarized. Disposition and reason for study discontinuation will also be provided as a by-participant listing.

8.7.5. Demographics And Baseline Characteristics Analysis

Demographics and baseline characteristics will be summarized using appropriate descriptive statistics.

8.7.6. Concomitant Medications/Therapies

All prior and concomitant medications recorded in the case report form will be coded to all matching Anatomic Therapeutic Classification codes using the most recent version of the WHO Drug Dictionary. Descriptive summaries will be prepared using the coded term. All concomitant medications recorded in the case report form will be listed.

8.7.7. Pharmacokinetic (PK) Analysis

The pharmacokinetic analyses and estimation of PK parameters will be performed using non compartmental methods using Phoenix® WinNonlin 8.3.1 or above.

8.7.8. Safety Analyses

8.7.8.1. Adverse Events

Adverse events will be classified by system organ class (SOC) and preferred term (PT) according to the most recent version of MedDRA dictionary.

TEAE are defined as adverse events with onset date on or after the first treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

a) Overall (i.e., regardless of severity or relationship to treatment)

b) Adverse events by severity

c) Related adverse events by severity

d) Adverse events leading to treatment discontinuation by severity

e) Adverse events leading to death by severity

8.7.8.2. Clinical Laboratory Data

Tabulations of raw data and change from baseline values will be presented by time point for each lab parameter. Tabulations will include the number of observations, mean, standard deviation, median, and minimum and maximum values. Abnormal laboratory results will be listed and summarized.

8.7.8.3. Vital signs

Tabulations of raw data and change from baseline values will be presented by time point for each vital sign parameter. Tabulations will include the number of observations, mean, standard deviation, median, and minimum and maximum values.

8.7.8.4. Physical Examination

Physical Examination findings will be presented as by-participant listing.

8.7.8.5. 12-lead ECG

Tabulations of raw data and change from baseline values will be presented by time point for each 12-lead ECG parameter. Tabulations will include the number of observations, mean, standard deviation, median, and minimum and maximum values.

8.7.8.6. Other Safety Data

All data from other tests such as unscheduled tests will be presented as a by-participant listing and/or summarized.

9. SAFETY REPORTING

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs as detailed in this Section of the protocol.

9.1. ADVERSE EVENT (AE) DEFINITION

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.

9.2. REPORTING OF ADVERSE EVENTS (AES)

The Investigator will then record all relevant AE/SAE information in the eCRF. All AEs will be collected from the time of dose administration until the safety follow-up visit. Medical occurrences that occur before the start of the study treatment, but after obtaining the ICF will be recorded in the Medical History section of the eCRF and not in the AE section, unless considered related to the study procedures. All events will be followed to resolution or until the participant completes the study. A final assessment of outcome will be made at that time.

All AEs must be recorded in the participant's medical records and on the CRF. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is considered to be a SAE (see Section 9.3), the impact the event had on study treatment (see Section 9.2.1), the Toxicity Grading Scale (intensity) of the event (see Section 9.2.2), the causality of the event (see Section 9.2.3), whether treatment is given as a result of the event (see Section 9.2.4), and the outcome of the event (see Section 9.2.5).

9.2.1. Impact on Study Treatment

The impact the event had on the study treatment will be assessed as either: dose increased, dose not changed, dose rate reduced, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown. The "not applicable" assessment will be used only when the participant is no longer in the Treatment Phase of the protocol.

9.2.2. Toxicity Grading Scale (Intensity) Assessment

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 to appendix 1.

9.2.3. Event Causality Assessment

AEs will be assigned a relationship (causality) to the study treatment. The Investigator will be responsible for determining the relationship between an AE and the study treatment. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study treatment. Relationship of AEs to study treatment will be classified as follows:

1. **Definitely related**: This category applies to those AEs that the Investigator feels are incontrovertibly related to the study treatment. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not be reasonably explained by the known characteristics of the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant; (3) it follows a known response pattern to treatment with the study treatment.
2. **Probably related:** This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study treatment. An AE may be considered probable if or when (must have three): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by participant's clinical state, environmental or toxic factors, or other therapies administered to the participant. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.
3. **Possibly related**: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are judged unlikely but cannot be ruled out with certainty to the study treatment. An AE may be considered possible if or when (must have two): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by participant's clinical state, environmental or toxic factors, or other therapies administered to the participant. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.
4. **Unlikely related**: In general, this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged likely to be unrelated to the study treatment. An AE may be considered unlikely if or when (must have two): (1) it does not follow a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by participant's clinical state,

environmental or toxic factors, or other therapies administered to the participant. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It does not follow a known response pattern to treatment with the study treatment.

5. **Unrelated**: This category applies to those AEs which, after careful consideration at the time they are evaluated, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and determined with certainty to have no relationship to the study treatment.

9.2.4. Treatment Given as a Result of the Event

The event impact in terms of treatment provided will be as either: none, medication administered, non-drug therapy administered, surgery performed, hospitalization, or other (with a specification).

9.2.5. Event Outcome Assessment

The outcome of the event will be assessed as either: fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, or unknown. Only one AE per participant is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given participant, only the primary cause of death will have an outcome of death.

9.3. Serious Adverse Event (SAE) Definition

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.

9.4. Reporting of Serious Adverse Events (SAEs)

The Investigator is required to report all SAEs that occur during the time period specified in Section 9.2. Once the Investigator becomes aware of an SAE, he/she must report the SAE to Safety Contact/Sponsor within 24 hours. The fax number or email address for reporting SAEs can be found in the protocol-specific Safety Management Plan.

The Safety Contact/Sponsor may request additional supporting documentation as it becomes available, such as lab reports, 12-lead ECG reports, discharge summary, hospital notes, etc., if applicable. Additional follow-up information as it becomes available must be reported to the Medical Monitor.

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

9.4.1. SAE Follow-Up

All participants experiencing an SAE, including the discontinued participants, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the Investigator or the last study visit, whichever occurs first (i.e., recovery, return to baseline status, no further improvement expected, or death).

For each SAE indicated as an unresolved event on the initial report, regardless of whether the participant completed the study or withdrew, the site should submit a follow-up report with updated information.

9.5. PREGNANCY REPORTING

To ensure participant safety, any pregnancy that occurs while participant is taking study drug should be recorded using a Pregnancy Notification Form and reported immediately to Sponsor within 24 hours of learning of the pregnancy.

If a participant becomes pregnant during the study before the end of treatment period, they will be a discontinued participant. If a participant becomes pregnant during the study after the end of treatment during the follow up portion, they can complete the remaining scheduled follow up unless there is a medical contraindication.

9.5.1. AE and SAE Reporting

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs.

9.5.1.1. Abortions

An induced elective abortion to terminate a pregnancy without medical reason is not regarded as an AE. However, an induced therapeutic abortion to terminate a pregnancy because of complications or medical reasons must be reported as an SAE. The underlying medical diagnosis for this procedure should be reported as the SAE term. A spontaneous abortion in a study participant is always considered an SAE.

9.5.2. Informed Consent

The ICF will include information regarding reporting of pregnancy to the Sponsor and collection of information through the end of pregnancy that occurs in a female participant. If a female partner becomes pregnant, the Investigator will request consent from the partner to collect this information.

9.5.3. Pregnancy Follow-Up

The pregnancy will be followed-up to determine the outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) and should include an assessment of the possible relationship to the study treatment of any pregnancy outcome. This information should also be documented on the Pregnancy Outcome Form and reported to the Sponsor.

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10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Participants will be identified on CRFs by a unique participant identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The participant identification number will be used if it becomes necessary to identify data specific to a single participant.

The local IRB, FDA, the monitors, auditors and personnel authorized by the Sponsor are eligible to review the medical and research records related to this study as part of their responsibility to protect human participants in clinical research. They will be given direct access to source data and documentation (e.g., medical charts/records, printouts etc.) for source data verification, provided that participant confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy. Each site will be required to ensure access while remaining compliant with institutional requirements.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. MONITORING REQUIREMENTS

The specific obligations outlined in 21 Code of Federal Regulations (CFR) and ICH guidelines require the Sponsor to maintain current personal knowledge of the progress of a study. Therefore, the Sponsor's designated monitor will visit the site during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

As delineated above, the Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all CRFs and corresponding study participant original medical records (source documents) at regular intervals throughout the study. Participant original medical records and other relevant data must be available to support all data recorded in the CRF. In addition to the original medical records, these data may include but are not limited to study, laboratory reports, etc.

In accordance with federal regulations, site inspections will serve to verify strict adherence to the protocol and the accuracy of the data that is being entered on the case report forms. A Monitoring Log will be maintained at each study site. The Monitoring Log will be signed by the monitor, dated and stated the type of visit. The Investigator should be aware that the study site and participant records may be inspected by the Sponsor and or representatives of the designated CRO, FDA or other regional regulatory authority.

11.2. ACCEPTABILITY OF CASE REPORT FORMS (CRFS)

For each participant who has signed an informed consent form, a CRF must be completed. For participants who are screen failures, this would be limited to the screen failure CRF page. All source documents and CRFs will be completed as soon as possible after the participant's visit and corrections to data on the CRFs will be documented, if applicable. The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. CRFs will be reviewed by the Sponsor’s or designated CRO’s monitor, who will make a decision as to their acceptability.

11.3. MODIFICATION OF PROTOCOL

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator’s IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the participant; or

2. When the modification does not involve the participant's participation in the study.

An amendment may also require modification of the informed consent form. The Investigator will provide an approval letter for the amendment and revised informed consent form, if applicable, to the Sponsor. An amendment must be provided in writing and it must be dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to FDA and other appropriate regulatory authorities and notify other Investigators using this protocol.

11.4. REPORTING PROTOCOL DEVIATIONS

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the participant will continue in the study. The Sponsor also has the right to discontinue the participant for protocol violations. The IRB may also have to be contacted if safety to the participant or if the scientific soundness of the study is involved. All protocol deviations must be documented in the CRFs.

11.4.1. Major Protocol Deviation or Violation

A major protocol deviation or violation is a deviation from the IRB approved protocol that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. Examples of this include:

- Failure to obtain informed consent prior to initiation of study-related procedures
- A research participant does not meet the protocol's eligibility criteria but was enrolled without prior approval from the sponsor.
- A research participant received the wrong treatment or incorrect dose.
- A research participant met withdrawal criteria during the study but was not withdrawn.
- A research participant received a prohibited concomitant medication.
- Failure to treat research participants per protocol procedures that specifically relate to primary efficacy outcomes.
- Changing the protocol without prior sponsor and IRB approval.
- Multiple minor violations of the same nature after multiple warnings.

11.4.2. Minor Protocol Deviation or Violation

A minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which DOES NOT have a major impact on the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Examples of this include:

- Follow-up visits that occurred outside the protocol required time frame because of the participant's schedule.
- Blood samples obtained at times close to but not precisely at the time points specified in the protocol.

12. ETHICS AND REGULATORY REQUIREMENTS

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, GCP, 21 CFR, ICH E6, HIPAA regulations in 45 CFR Part 164 (US only), and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without the prior review and approval of the IRB, except when the modification does not involve the participant's participation in the study or where it may be necessary to eliminate an immediate hazard to research participant. In the latter case, the change will be reported to the IRB as soon as possible, according to IRB regulations.

Additionally, the study product used in this study is manufactured, handled and stored in accordance with applicable GMP. The study product provided for this study will be used only in accordance with this protocol.

12.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

The Principal Investigator (PI) at each site will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, informed consent form, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the participants or when the modification does not involve the participant's participation in the study.

12.2. INVESTIGATOR'S RESPONSIBILITIES

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations.

12.3. PARTICIPANT INFORMED CONSENT REQUIREMENTS

All participants participating in this study will be given to by the Investigator and/or designee, written and oral information about the study in a language understandable by the participant. Written informed consent will be obtained from each participant prior any procedures or assessments that would not otherwise be required for the care of the participant are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the participant has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

The written Informed Consent Form (ICF) will be in compliance with CFR 21 Part 50.27 and GCP guidelines. The Sponsor and/or designated CRO will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the study. The study site must provide the Sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the participant's study records, and a copy is provided to the participant. A second copy may be filed in the participant’s medical record, if allowed by institutional policy.

13. DATA HANDLING AND RECORD KEEPING

13.1. RECORDING AND COLLECTION OF DATA

The primary source document for this study will be the participant's medical record. If separate research records are maintained by the Investigator(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to approve case report forms (CRF). The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and CRFs will be completed as soon as possible after the participant's visit.

The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. Designated source documents will be signed and dated by the appropriate study personnel. The Investigator must agree to complete and maintain source documents and CRFs for each participant participating in the study.

All research data will be entered, either electronically or manually, into a computerized database. The clinical database will be designed by the clinical data manager in accordance with 21 CFR Part 11 and based on protocol requirements defined by the Sponsor in association with the Lead Investigator.

The Investigator will maintain a confidential list of study participants that will include each participant’s study number, name, date of birth, and unique hospital identification number if applicable. This list will be kept by the Investigator and will not be collected by the Sponsor. A notation will be made in the participant’s case history/medical chart that he/she is participating in a clinical study and has provided a signed and dated ICF as well as a release for protected health information as required by local policies. The Investigator must also maintain a separate screening log of all the participants screened for participation in the study; it should include gender, age, eligibility status, reason for ineligibility, if applicable; and study allocated participant number, if applicable.

13.2. CLINICAL DATA MANAGEMENT

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor’s or CRO’s standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor’s or the CRO’s SOPs as well as provisions of the study-specific Data Management Plan.

13.3. ARCHIVING

All study documentation at the Investigator site and Sponsor site will be archived in accordance with ICH GCP E6 and the Sponsor's quality standards and SOPs.

The Investigator will maintain all research records, reports, and case history reports for a period of two (2) years after regulatory approval of the investigational product. If no application is filed or if the application is not approved, records must be maintained for two (2) years after all investigations have been completed, terminated or discontinued and the FDA has been notified.

These documents should be retained for a longer period however, if required by the applicable regulatory requirements or if needed by Sponsor or its authorized representative (as per GCP 5.5.11).

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are participant to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., participant's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study)
- Completed CRFs
- Signed protocols and protocol amendments
- Laboratory results, ranges, and certifications
- IP and accountability records
- Study personnel signature log
- Monitoring logs
- Correspondence to and from the Sponsor, designee and IRB
- Principle Investigator and sub-investigator CVs
- Signed informed consent and protected health information consent forms
- Participant screening
- SAE reports
- IRB approval and re-approval letters
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

Study records should not be transferred from site or destroyed without prior written agreement between the Sponsor and the study Investigator. Study records are participant to inspection by applicable health and regulatory agencies at any time.

14. PUBLICATION PLAN

All information supplied by Oneness Biotech Co., Ltd. in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, clinical protocol, case report forms and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of Oneness Biotech Co., Ltd., shall not be disclosed to others without the written consent of Oneness Biotech Co., Ltd., and shall not be used except in the performance of this study.

It is understood by the Investigator that the Sponsor will use the information collected in this clinical study in connection with the development of the investigational product. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities. By agreeing to participate in this clinical study, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this study.

Publication and Disclosure: The site and Investigator agree to submit any proposed manuscript, presentation or other public disclosure regarding the study to Sponsor for review at least thirty (30) days prior to submitting such proposed manuscript to a publisher or delivering or making such presentation or other public disclosure to any third party. Within thirty (30) days of its receipt, Sponsor shall advise the site and/or Investigator, as the case may be, in writing of any information contained therein that is confidential information (other than research results included in a proposed manuscript) or that may impair Sponsor's ability to obtain patent protection. Sponsor shall have the right to require the site and/or Investigator, as applicable, to remove specifically identified confidential information (but may not require removal of research results from a proposed manuscript) and/or to delay the proposed submission or delivery of the proposed manuscript or presentation, or other public disclosure, for an additional sixty (60) days to enable Sponsor to seek patent protection. The site and Investigator shall not publish, publicly disclose, present or discuss any results of or information pertaining to the site's and Investigator's activities prior to completion of the study, even if the study is terminated before its completion and the final clinical study report is signed off, or with respect to any endpoints or analyses other than those specified in this protocol.

15. REFERENCES

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16. APPENDIX

16.1. APPENDIX 1: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

For complete detailed information please refer to the link below:
https://www.fda.gov/media/73679/download

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (° C) ** (° F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension

Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily	ER visit or hospitalization

			activity	
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – Hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes –	1.1 – 1.5 x	1.6 – 2.0 x	2.1 – 5.0 x	> 5.0 x ULN

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
amylase, lipase	ULN	ULN	ULN	

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm3	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	> 25,000
WBC Decrease - cell/mm3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm3	125,000– 140,000	100,000– 124,000	25,000–99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated

				intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal
parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** “ULN” is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.