CLINICAL STUDY PROTOCOL

PROTOCOL TITLE: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of INB03 in the Treatment of Participants with Pulmonary Complications from Coronavirus Disease (COVID-19)

PROTOCOL NUMBER: INB03-COVID-19_01

CLINICAL TRIAL PHASE: Phase 2

COMPOUND NAME: INB03

SPONSOR: INmune Bio Inc.
1200 Prospect Street, Suite 525
La Jolla, CA 90237

CURRENT VERSION: Version 13.0 – 07 October 2021

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PROTOCOL APPROVAL SIGNATURE

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This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

RJ Tesi MD
INmune Bio Inc.
1200 Prospect Street, Suite 525
La Jolla, CA 90237

Signature: _____

Date: _____

STATEMENT OF COMPLIANCE

The investigator will conduct this study as detailed herein, in compliance with current standards for the ICH and GCP and the applicable regulatory requirements and will make every reasonable effort to complete the study within the time designated.

The investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Human Research Ethics Committee (HREC)/Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study patients.

This document contains information that is privileged or confidential. As such, it may not be disclosed unless specific prior permission is granted in writing by the sponsor or such disclosure is required by federal or other laws or regulations. Persons to whom any of this information is to be disclosed must first be informed that the information is confidential. These restrictions on disclosure will apply equally to all future information supplied, which is indicated as privileged or confidential.

The investigator agrees that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Institution Name: _____

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LIST OF ABBREVIATIONS

ADA	Anti-drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
BCG	Bacillus Calmette-Guérin
BIPAP	Bi-level Positive Airway Pressure
CCR5	C-C Chemokine Receptor Type 5
CCU	Cardiac Care Unit
CHF	Congestive Heart Failure
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CRP	C-Reactive Protein
CS	Cytokine Storm
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ePRO	Electronic Patient-Reported Outcome
FAS	Full Analysis Set
FiO2	Fraction of Inspired Oxygen
GAS	Group A Streptococcus
GCP	Good Clinical Practice

HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Viruses
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICAM	Intercellular Adhesion Molecules
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IRB	Institutional Review Board
IL	Interleukin
ITT	Intent-to-Treat
IV	Intravenous
LCQ	Long COVID Questionnaire
LCIQ	Long COVID Informant Questionnaire
LPS	Lipopolysaccharide
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NOAEL	No-Observed-Adverse-Effect-Level
OVA	Ovalbumin
PaO2	Partial Pressure of Oxygen (Arterial)
PHQ-9	Patient Health Questionnaire-9
PICF	Participant Information and Consent Form
PO	By Mouth
PPS	Per-Protocol Set
SAE	Serious Adverse Event
SaO2	Room Air Oxygen Saturation
SAP	Statistical Analysis Plan

SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Subcutaneous
SD	Standard Deviation
SOA	Schedule of Assessments
SOC	Standard of Care
SpO2	Peripheral Capillary Oxygen Saturation
SS	Safety Set
sTNF	Soluble Tumour Necrosis Factor
TEAE	Treatment Emergent Adverse Event
tmTNF	Transmembrane Tumour Necrosis Factor
TNF	Tumour Necrosis Factor
TNFR	Tumour Necrosis Factor Receptor
ULN	Upper Limit of Normal
VCAM	Vascular Cell Adhesion Molecules
WBC	White Blood Cell
WCBP	Women of Childbearing Potential
WHO	World Health Organization

SYNOPSIS

Name of Sponsor/Company:	INmune Bio Inc
Protocol Number:	INB03-COVID-19_01
Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of INB03 in the Treatment of Participants with Pulmonary Complications from Coronavirus Disease (COVID-19)
Investigational Product:	INB03
Study Centre(s):	Multiple sites in United States and Australia
Development Phase:	Phase 2
Objectives:	Primary Objective • To evaluate if INB03 given as a SC injection can decrease disease progression defined as death or requirement for mechanical ventilation in participants with pulmonary complications from COVID-19 infection. Secondary Objectives • To assess the effect INB03 has on all-cause mortality in participants with pulmonary complications from COVID-19 infection; • To determine if INB03 can decrease non-respiratory catastrophic complications of COVID-19 infection including admission to ICU, new onset neurologic, cardiovascular or thromboembolic disease, or renal failure; • To evaluate if treatment with INB03 reduces increase in the WHO Ordinal Scale for Clinical Improvement score; • To evaluate if length of hospital-stay in participants with pulmonary complications from COVID-19 infection decreases when treated with INB03; • To evaluate the safety and tolerability of INB03 when given to participants with pulmonary complications from COVID-19 infection; • To assess the effect INB03 has on inflammatory markers in participants with pulmonary complications from COVID-19 infection. Exploratory Objectives • To qualitatively and quantitatively evaluate the presence and nature of residual (post-Study Day 40) complaints of fatigue, malaise, affective symptoms, inflammatory cognitive dysfunction syndrome and associated functional limitations.
Methodology:	The trial is a Phase 2, double-blind, randomized, placebo-controlled clinical trial of INB03 in participants with pulmonary complications

	due to COVID-19 infection. Each participant will complete up to 6 study visits. **Screening:** Participants with a diagnosis of COVID-19 will be screened for study eligibility. Prior to any trial related procedures, participants will provide their consent to participating in the clinical trial. Screening assessments will include: • collection of medical history/participant demographics (including race and ethnicity); • physical examination (including vital signs, height and weight); • room air oxygen saturation (SaO2), if possible; • chest imaging; • electrocardiogram (ECG); • WHO Ordinal Scale for Clinical Improvement (to be completed any time after informed consent is obtained and up to 1-hour post-randomization on Day 1); • clinical laboratory evaluations (as per Table 2: Clinical Laboratory Evaluations); • serum or urine pregnancy test for women of childbearing potential (WCBP). If any of the above assessments are performed as part of routine clinical care within 1 day of Screening, they do not need to be repeated. **Study Day 1:** Eligible participants will be randomized to receive either INB03 at 1mg/kg by subcutaneous injection (SC) + standard of care (SOC) or Placebo SC injection + SOC within 1 day of Screening. Participants will receive their first dose of study drug after randomization. Blood samples to check tumour necrosis factor (TNF) levels and perform an anti-drug antibody (ADA) test will be collected before dosing. Clinical assessments while participants are inpatients will be as per routine management of hospitalized COVID-19 patients including daily collection of vital signs, physical exam, concomitant medications and laboratory evaluations. 12-lead ECGs and chest imaging assessments will be performed if deemed clinically necessary. Additionally, use of non-mechanical ventilation will be collected daily until the participant is discharged from hospital. The WHO Ordinal Scale will also be completed daily until the participant is discharged from hospital. Since SOC may change over time, concomitant medications will be collected for the duration of the study. **Study Day 8:** Participants will be given a second dose of INB03 or Placebo on Day 8 (7 days after randomization) if the participant remains in the hospital. Clinical assessments while participants are inpatients will continue as per routine management of hospitalized

	COVID-19 patients and described in Table 3 – the Schedule of Assessments (SOA). Since the timing of hospital discharge in this patient population cannot be predicted, discharge assessments will be obtained on the day the participant is to be discharged. If the participant remains in the hospital, the participant will continue with daily assessments as per Table 3 - SOA. At discharge, no additional follow-up is expected until the participant is seen for the Study Day 28 visit. **Study Day 28:** A follow-up visit will be conducted on Day 28. Follow-up study assessments will include: • physical examination (including vital signs); • room air oxygen saturation (SaO2) if possible; • chest imaging (if deemed clinically necessary); • ECG; • clinical laboratory evaluations (as per Table 2: Clinical Laboratory Evaluations); • adverse events; • assessment of disease progression and use of non-mechanical ventilation; • WHO Ordinal Scale for Clinical Improvement. If participant is still in hospital at Study Day 28, no additional follow-up is expected until the participant is seen on the Day 40 final safety visit. **Study Day 40:** A final visit will be conducted on Day 40. End of study safety assessments will be conducted as per Table 3 - SOA. **Study Day 40-50:** Participants will complete Long COVID questionnaires using an electronic Patient-Reported Outcomes (ePRO) portal. A separate questionnaire (the Informant questionnaire) will be completed by a family member or friend, who is familiar with the participant's COVID-19 symptoms, in person at the Study Day 40 visit or by phone. A separate informed consent form will be collected from the family member or friend prior to completion of this questionnaire. **Study Day 50-70:** In a subset of participants who report Long COVID symptoms, a telephone interview will be conducted to qualitatively and quantitatively evaluate the presence and nature of residual or emergent complaints of fatigue, malaise, affective symptoms, inflammatory cognitive dysfunction syndrome and associated functional limitations. **Study Day 70:** Participants will be contacted via telephone on Day 70 to assess AEs and changes in concomitant medications. Adverse events (AEs) will be monitored for all participants who are randomized until Study Day 70.

Number of subjects:	Up to 366 participants will be randomized 1:1 to INB03 + SOC or Placebo + SOC.
Inclusion Criteria:	To be eligible for study entry, participants must satisfy all of the following criteria at Screening: 1. Have one or more of the following comorbidities: a. Age ≥ 65 years; b. Obesity (BMI ≥ 30); c. Hypertension (on one or more drugs for treatment of hypertension); d. Diabetes (on one or more drugs for Type I or Type II diabetes); e. Cardiovascular disease (on one or more drugs for treatment of cardiovascular disease, other than aspirin); f. History of congestive heart failure (CHF) or myocardial infarction (MI); g. Black or African-American race (at least one parent identifies as Black or African-American); h. Hispanic or Latino ethnicity. 2. Have a positive COVID-19 test in the last 28 days; 3. Have room air SaO2 < 96%, or SpO2 < 96% on room air at sea level, or PaO2/FiO2 < 300; 4. Have abnormal chest X-ray, MRI or CT scan consistent with pulmonary complications from COVID-19; 5. Provide written informed consent prior to any study related procedures being performed.
Exclusion Criteria	Participants will be excluded from the study if 1 or more of the following criteria are applicable at Screening: 1. Age < 18 years; 2. Require immediate intubation due to advanced respiratory failure - including continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BIPAP); 3. Require immediate admission to an Intensive Care Unit (ICU) for any reason; 4. On therapy with approved TNF inhibitor (eg: infliximab, etanercept, adalimumab, certolizumab pegol, golimumab, thalidomide, etc) in the last 6 months; 5. Being treated with dexamethasone (IV or PO) at a dose of >15mg per day or solumedrol or equivalent corticosteroid at a dose of >120mg per day;

	6. Taking any medication known to be CCR5 receptor antagonist (eg: leronlimab, aplaviroc, vicriviroc or maraviroc) in the last 6 months; 7. Taking any medication known to inhibit the cytokine pathway (eg: anakinra, tocilizumab, siltuximab, etc) in the last 6 months; 8. Known to be pregnant; 9. Has known HIV, HCV or HBV infection; 10. Has known Mycobacterium tuberculosis infection or evidence of infection on chest X-ray; 11. Significant hepatic disease (ALT/AST> 4 times the ULN); 12. On therapy for cancer in the last 6 months; 13. On therapy for organ transplant in the last 6 months or on a waiting list for organ transplant, including patients on renal replacement therapy for any reason; 14. Known hypersensitivity to investigational product or its excipients; 15. Participating in an investigational drug or device trial; 16. Congestive heart failure (CHF) or myocardial infarction (MI) diagnosed in the last 2 months.
Test Product, Dosage and Mode of Administration:	INB03 is a pegylated protein variant of soluble tumour necrosis factor (sTNF). Placebo will be normal saline. The clinical trial will have two treatment arms - INB03 + SOC or Placebo + SOC. Approximately 183 participants will be randomized to each arm in a blinded fashion. All participants will receive a single dose of study drug by SC injection immediately upon randomization. Participants randomized to receive INB03 will receive INB03 1mg/kg (up to a maximum dose of 90mg) and participants randomized to Placebo will receive a SC injection of normal saline. A second dose of INB03 1mg/kg or Placebo by SC injection will be administered on Study Day 8 to participants who remain in hospital. There is no need for pre-medication. Participants should be observed for 30 minutes after the first dose of study drug.
Duration of Study:	The study will be 71 days in duration; 1 day for screening and 70 days in study for efficacy and/or safety evaluations.
Criteria for Evaluation:	<u>Primary Endpoint:</u> • Proportion of participants with disease progression from randomization to 28 days post-randomization, where disease progression is defined by the development of need for mechanical ventilation or death. Mechanical ventilation

	includes CPAP, BIPAP or mechanical ventilation requiring intubation. Secondary Endpoints: • Proportion of participants with all-cause mortality; • Proportion of participants who transfer to ICU level care by Day 28 (ICU level care is defined as a hospital setting where patient to nurse ratio is < 4); • Proportion of participants with a new onset of neurologic disease (requiring medical intervention), including stroke by Day 28; • Proportion of participants with evidence of new CHF or new MI requiring medical intervention by Day 28; • Proportion of participants with a new onset embolus or thrombus by Day 28; • Proportion of participants who develop a need for renal replacement therapy (defined as need for any type of dialysis including intermittent or continuous peritoneal or hemodialysis) by Day 28; • Proportion of participants with an increase in the WHO Ordinal Scale of Clinical Improvement score at any time during the study; • Length of hospital stay defined as the number of days in hospital from time of randomization to time of discharge or death, whichever occurs first; • Change from baseline in inflammation markers over time. Safety Endpoints: • Incidence of adverse events and serious adverse events not due to underlying disease; • Incidence of abnormal findings in clinical safety laboratory parameters, vital signs, and ECGs. Exploratory Endpoints: • Percentage of participants who report Long COVID symptoms; • Total score on the Patient Health Questionnaire-9 (PHQ-9); • Total and subscale scores on Long COVID Questionnaire (LCQ); • Total and subscale scores on Long COVID Informant Questionnaire (LCIQ).

Sample Size:	Sample size was calculated on the assumption that participants who meet the enrollment criteria progress to respiratory failure or death 21% of the time given current SOC. Therapy with INB03 is expected to decrease disease progression by two-thirds to 7%. Assuming 90% power and a one-sided alpha level of 0.005, N=346 (173 per arm) are required to observe the expected treatment effect. Assuming approximately 5% of participants are randomized but do not receive treatment, a total of 366 will be randomized to ensure 346 participants receive study drug. Additionally, an interim analysis for futility will be performed when approximately 20% of participants required to observe the expected treatment effect complete the Study Day 28 visit (N~70). Participants evaluated in the interim analysis include those who are randomized and receive study drug and have the Day 28 assessment or who had an intercurrent event prior to Day 28 with early termination (ie: withdrawal of consent, lost to follow-up). A preliminary analysis of the primary efficacy data will be performed prior to final database lock.
Statistical Methods	<u>General Methodology:</u> All enrolled participants who are randomized to a study treatment arm will be included in the Intent-to-Treat (ITT) population. The modified ITT (mITT) population is defined as participants who are included in the ITT population who also receive any amount of study drug. The mITT population is the primary analysis population for efficacy analyses. In general, continuous variables will be summarized using number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be tabulated with frequency counts and percentages. Where appropriate, 95% confidence intervals (CIs) will be provided. All data will be listed. <u>Efficacy Analysis:</u> The population of interest for all primary and secondary efficacy estimands include participants who are randomized, who have been diagnosed with COVID-19, have at least one co-morbidity, are admitted to the hospital, have pulmonary complications due to COVID-19 and who have received any amount of study drug. This population is considered the mITT population. All primary and secondary efficacy estimands will be evaluated at time of randomization to Study Day 28. Pairwise comparisons between study treatments INB03 + SOC and Placebo + SOC will be performed for each primary and secondary endpoint. The analysis model for the primary endpoint of proportion of participants with disease progression will use a stratified Cochran-Mantel-Haenszel (CMH) test stratified by age (<50, 50-65, >65) and number of co-morbidities (1, 2, 3+) to compare the failure rates of

	INB03 vs. Placebo. The primary endpoint treatment comparison will be evaluated using a one-sided alpha=0.005 significance level. The odds ratio and corresponding 95% confidence intervals will be provided. A supportive analysis will be performed using logistic regression with treatment and covariates of age and co-morbidities at baseline included in the model. Additional covariates may be added to the model and defined in the SAP. Sensitivity and supplementary analyses will also be performed and are described in the protocol. Binary secondary endpoints will be analyzed similarly to the primary endpoint using a CMH test, and continuous secondary endpoints, such as length of hospital-stay and change from baseline in inflammatory markers, will be analyzed using an analysis of covariance (ANCOVA) model and will include treatment and covariates such as age and number of co-morbidities. Exploratory endpoints will be summarized by treatment group and may be analyzed similarly as the primary and secondary endpoints. Analysis of interview data collected on a subset of participants will be summarized in a separate report. <u>Interim Analysis:</u> An interim analysis will be performed when approximately 70 participants who meet the mITT population definition and have completed the Study Day 28 visit or who had an intercurrent event prior to Day 28. In order to maintain study blind, an independent unblinded statistical team will perform the analyses and present the results to the data monitoring committee (DMC). The primary efficacy endpoint will be analyzed and a limited number of individuals who are not involved in the study conduct or review of day-to-day activities of the study will be informed on the unblinded efficacy results in order to plan further development and inform on other corporate objectives. The DMC will also review unblinded safety and the primary efficacy data and recommend to the sponsor their unbiased opinion concerning safety and efficacy of INB03 in an acute COVID population. <u>Safety Analysis:</u> Safety data including AEs, vital sign measurements, ECGs, clinical laboratory information, and concomitant medications will be summarized descriptively for the safety population by treatment arm and overall. The safety set is defined as all randomized participants who have received any amount of study drug. AEs will be coded using the Medical Dictionary for Regulated Activities (MedDRA) classification system and summarized by System Organ Class and Preferred Term. For parameters measured over time, absolute values and changes from baseline will be summarized for each time point.

	Baseline is defined as the parameter value taken prior to randomization.
Data Monitoring Committee	A data monitoring committee (DMC) will assess ongoing safety at pre-specified time points as detailed in the DMC charter. The DMC will also review unblinded efficacy and safety data at the time of the interim analysis.

1 INVESTIGATIONAL TEAM

Refer to the Study Contact List maintained in the Investigator Site File for details of investigators, sponsor personnel, clinical research organisation personnel and facilities used in the study.

2 INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Coronavirus (COVID-19) Disease

Coronavirus (COVID-19) disease is a highly infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is responsible for an ongoing pandemic with more than 57.8 million cases of COVID-19 having been reported in over 188 countries and territories, resulting in approximately 1.3 million deaths as of 22 November 2020 (WHO COVID-19 Weekly Epidemiological Update). Symptoms of the disease, including respiratory complications, appear to be most severe in older individuals, and those with co-morbidities such as obesity, diabetes, chronic respiratory disease, kidney or liver disease, immunosuppression and cancer.

Approximately 20% of patients who contract COVID-19 report long-term symptoms after their acute COVID symptoms, termed 'long COVID' patients. These long-COVID patients report multiple somatic and neurological symptoms. According to the CDC, the most commonly reported symptoms are dysautonomia, fatigue, shortness of breath, cough, joint pain, chest pain, difficulty with thinking/concentration ("brain fog") and depression. These symptoms are seen even in patients who were not hospitalized or only had a mild illness (Tenforde *et al.* 2020).

2.1.1 Treatment of Respiratory Complications to COVID-19

The pulmonary complications of SARS-CoV-2 infection are not driven by direct infection of pulmonary tissue by the virus but by cytokines (cytokine storm; CS) from an aberrant and uncontrolled immune response to the viral infection (Guo *et al.* 2020). Elimination and/or control of the CS should decrease pulmonary complications and improve survival. While the source of the pulmonary pathology is clear, it is not yet known if the associated cardiovascular, renal and neurologic complications associated with COVID-19 are due to the CS or direct infection of these tissues by the virus.

Pro-inflammatory cytokines including tumor necrosis factor (TNF), interleukin-6 (IL-6), and IL-1 all play a significant role in CS. Of these, TNF sits at the apex of the inflammatory response in acute viral disease and induces IL-6/IL-1(Tisoncik *et al.* 2012, Wojdasiewicz *et al.* 2014). Inflammation and cell death are driven by soluble TNF (sTNF), not transmembrane TNF (tmTNF), which is necessary for immunocompetence. Aberrant levels of sTNF can cause CS and numerous studies have suggested anti-TNF drugs may provide therapeutic benefit (Tisoncik *et al.* 2012, D'Elia *et al.* 2013, Liu *et al.* 2016, Clark and Vissel 2017, Zhou *et al.* 2020). Consistent with this profile, levels of sTNF are increased in both the blood (Guo *et al.* 2020) and lungs (Shi *et al.* 2020) of patients with severe COVID-19 with pulmonary complications. sTNF activates endothelial cells to upregulate intercellular adhesion molecules (ICAM) and vascular cell

adhesion molecule (VCAM) to promote transmigration of leukocytes from the lumen of blood vessels (Sawa *et al.* 2007). Within the lung, sTNF activates leukocytes causing edema and tissue destruction (Mazzon and Cuzzocrea 2007).

Immunosuppressive treatments to manage acute respiratory distress (ARDS) in COVID-19 patients can have grave consequences as was observed with increased death following corticosteroid treatment (Shang *et al.* 2020). Current treatment strategies such as anti-IL-6 therapies are also immunosuppressive which could impair the ability of the immune system to clear the viral infection or increase the risk of secondary infection. Notably, secondary bacterial infection was observed in more than half of deceased COVID-19 patients (Zhou *et al.* 2020). Viral shedding has been reported for up to eight days after symptoms disappear in more than half of patients and even longer in the more patients with severe disease (Chang *et al.* 2020). Whether or not immunosuppressive therapies extend viral shedding is unknown although patients with severe disease are more likely to receive immunosuppressive treatment.

2.1.2 Clinical Trial Rationale

Selectively neutralizing sTNF will have several benefits. sTNF is the cytokine that both promotes transmigration of leukocytes from the blood vessel to the lung parenchyma and stimulates the cytokine secretion of leukocytes in the tissue that causes cell damage and edema resulting in hypoxia. Neutralization of sTNF will prevent leukocyte infiltration of pulmonary tissue and decrease inflammation of cells already in the extracellular compartment. Because of the need to stop the CS, early treatment is ideal to both prevent progression of pulmonary pathology to ARDS as long as the therapy does not compromise the immune response to the virus (Shi *et al.* 2020).

INB03 is a recombinant protein variant of the soluble form of native human TNF that has mutations engineered in the TNFR binding interfaces that eliminate its ability to bind to or activate TNFR1 and TNFR2. INB03 is a first-in-class agent that acts by a novel dominant-negative mechanism to eliminate pro-inflammatory sTNF homotrimers through exchange of monomeric subunits between the compound and the native cytokine. INB03 does not activate TNF-associated signalling pathways, acting only by exchanging subunits with sTNF, thereby destroying the biological activity of sTNF.

INB03 is not immunosuppressive. It has shown to reduce inflammation in multiple infectious disease models without compromising the immune response to infection or affecting mortality (Zalevsky et al. 2007, Olleros et al. 2009, 2010, Maillet et al. 2011, Vanwalleghem et al. 2017, Liu et al. 2019). INB03 can be given prophylactically to prevent disease progression without a negative effect on the ability of the immune system to fight the infection – viral and bacterial. These characteristics may even improve the ability of the patient to recover from ARDS.

Because the drug targets an important inflammatory cytokine that drives the development of pulmonary complications of COVID-19, is not immunosuppressive acutely (it does not worsen the immune response to bacterial or viral infection), is safe and well tolerated at the proposed dose and is simple to administer (up to 2 subcutaneous doses over a 8 day period), the proposed trial will target older patients who have a diagnosed COVID-19 infection with pulmonary complications. This is a high-risk group of patients that can deteriorate rapidly requiring

intensive care beds and increased respiratory support. INB03 is not an anti-viral therapy. Therapy is not expected to decrease viral load, ability of the participant to infect others or length of active infection or shedding. The goal of the study is to prevent symptomatic participants from getting worse. If INB03 can safely prevent progression of COVID-19 related symptoms so that participants do not end up requiring intensive care and ventilatory support, this should decrease mortality and decrease the intense resource pressures on the health care system.

The trial focuses on high risk adult patients. Many of these patients will have at least one co-morbidity (obesity, hypertension, cardiovascular disease, diabetes, Black/African-American race or Hispanic/Latino ethnicity). This population is most likely to develop complications of COVID-19 infection requiring admission to ICU including respiratory embarrassment. Younger patients do develop symptomatic disease, but they rarely progress to the point of requiring ventilatory support. Follow-up has been streamlined because much of the medical system is focused on inpatient care. Every attempt has been made to allow that focus to continue. As such, the trial is designed to simplify care of the patients during the surge of COVID-19 infections and hospital admissions.

In addition to the acute complications of COVID-19, a subset of patients will have persistent symptoms and become "long-haulers" (Rubin 2020, Greenhalgh et al. 2020). Although this is an emerging population with no strict definitions, these patients experience symptoms lasting beyond three weeks after recovery from acute COVID-19 (Greenhalgh et al. 2020). The emerging data on Long COVID patients suggests a high prevalence of symptoms such as dysautonomia, fatigue, cognitive, and mood, among others (Davis et al. 2020).

These core symptoms of Long COVID such as cognitive dysfunction, fatigue, and depression mirror sickness behaviors which are induced by pro-inflammatory cytokines, specifically TNF (Kelly and Kent 2020). To this end, COVID-19 triggers long-lasting changes in the immune system (Rubin 2020), suggesting that long-COVID symptoms are a consequence of immune dysfunction and subsequent chronic inflammation triggered by acute infection (del Rio et al. 2020, Greenhalgh et al. 2020).

To better understand the contribution of inflammation to the development of Long COVID symptoms, study participants will receive a series of questionnaires that address the most commonly reported symptoms that qualitatively and quantitatively evaluate the presence and nature of residual (post-Study Day 40) complaints of fatigue, malaise, affective symptoms, inflammatory cognitive dysfunction syndrome and associated functional limitations.

2.2 Nonclinical Studies of INB03

As mentioned in Section 2.1.2, the ideal therapy to treat ARDS in COVID-19 will quickly reduce inflammation in the lung without impairing the immune response needed to clear the virus. INB03 has been tested in multiple models of disease whose findings support its use to treat ARDS in COVID-19 patients. These studies are summarized below.

- In an animal model of allergic lung inflammation, INB03 reduced; i) the recruitment of inflammatory cells (lymphocytes and eosinophils), ii) levels of erythropoietin activity, iii)

inflammatory factors in the lung. INB03 suppressed ovalbumin (OVA)-induced airway hyperresponsiveness (Maillet *et al.* 2011).

- Multiple studies have shown that INB03 can reduce inflammation within hours of administration in rodents challenged with a variety of immunogens including; lipopolysaccharide (LPS), Group A Streptococcus (GAS) infection, and Bacillus Calmette-Guérin (BCG) infection. In a GAS model, INB03 reduced blood TNF protein levels at the earliest timepoint examined, 6 hours after treatment (Liu *et al.* 2019). Similarly, TNF, IL-6, and IFNg were significantly reduced 8 hours after BCG-infected mice were challenged with LPS (Olleros *et al.* 2010). INB03 has also been shown to significantly reduce neuroinflammation following GAS infection within 48 hrs (Liu *et al.* 2019) and LPS challenge within 3 hours (*unpublished data*).
- INB03 is not immunosuppressive in animal models of infectious diseases. Immunosuppressive treatments including the currently available TNF and IL-6 antagonists increase risk of infection and ability to fight infections. For instance, in an animal models of BCG and Mycobacterium tuberculosis infection, inhibition of TNF by etanercept, which blocks both tmTNF and sTNF, increased pulmonary infiltrate and bacterial load which culminated in 100% mortality by day 30. By contrast, Mycobacterium tuberculosis-infected mice treated with INB03 had fewer pulmonary lesions, a reduced bacterial load, and normal survival (Olleros *et al.* 2009). Similarly, mice given a sublethal Listeria infection and treated with etanercept had a 100% mortality within a week. Not only did 100% of mice treated with INB03 survive, immunity was maintained (low bacterial load and liver microabscesses) (Zalevsky *et al.* 2007). Interestingly, INB03 significantly improved mortality in mice infected with Group A Streptococcus (median survival 11.5 days) compared to infected mice treated without INB03 (median survival 4 days) (Liu *et al.* 2019). In parasitic disease, INB03 did not affect parasitic load or survival in mice infected with trypanosome parasitemia (Vanwalleghem *et al.* 2017). Recently, and in collaboration with the National Institutes of Health (NIH), INB03 has been tested in mice infected with Eastern Equine Encephalitis and Coxsackie virus B to determine whether INB03 increased mortality in viral infections (*unpublished data*). In each case, there was no impact on disease burden and survival further demonstrating that INB03 provides potent anti-inflammatory effects without suppressing the immune system's ability to fight infection.

Please refer to the INB03 Investigator's Brochure (IB) for data on the nonclinical pharmacokinetic and toxicokinetic studies of INB03 conducted to date in rats and monkeys.

2.3 Clinical Studies of INB03

Please refer to the INB03 IB for data on clinical studies conducted to date.

2.4 Known and Potential Risks

This will be the first study of INB03 in patients with pulmonary complications of COVID-19. However, INB03 has been well tolerated in pivotal toxicology studies conducted in rats and

cynomolgus monkeys. Until there is more data from human trials, all risks are potential and are based on animal data and events that have been noted with other TNF-antagonists.

Currently, INB03 is being evaluated as a potential therapeutic protein with a planned once a week SC injection in humans. As with any injected therapeutic protein, there is the potential for an anti-drug immune response. As a consequence, antibodies which develop in response to drug treatment (immunogenicity) to native TNF or INB03 is a critical safety concern and will be closely monitored throughout the clinical studies.

Injection or allergic reactions may occur. Precautions for anaphylaxis will be observed during INB03 administration.

2.5 Dose Justification

INB03 is delivered as a subcutaneous dose once-a-week. For this trial, the first dose will be administered on Study Day 1 and a second dose on Study Day 8 if participant remains in hospital. The dose planned in this Phase 2 study is 1mg/kg once a week by SC injection. The dosing decision is based on the mechanism of action, the pharmacology in a non-human primate model and human data for the completed Phase I study in oncology (refer to the INB03 IB). To effectively neutralize 99.99% of sTNF in blood, trough blood levels of drug must be at 2 logs least 2 logs greater than the TNF level in blood. TNF levels in blood rarely exceed 100pg/ml (Diao *et al.* 2020). Thus, a trough level of more than 10,000pg/ml is adequate. This is the trough level obtained in the oncology Phase I trial using 1mg/kg/week SC dosing.

The drug has extensive pre-clinical pharmacokinetic and pharmacodynamic testing that is part of FDA IND# 100,130 that was opened for the treatment of Rheumatoid arthritis. No dose limiting toxicity (DLT) was determined in those studies. A no-observed-adverse-effect-level (NOAEL) was determined in a rodent model as 10mg/kg per day. The pathology noted on the NOAEL was vacuolated macrophages at the injection site. This was thought to be caused by the PEGylation. The proposed dose of 1mg/kg once a week is 70 times lower than the NOAEL dose. Furthermore, this dose has been used in more than 9 human participants with a single case of injection site inflammation. Otherwise the drug has been well tolerated for up to 117 days (14 weeks).

3 OBJECTIVES AND PURPOSE

3.1 Primary Objective

The primary objective of the study is to:

- Evaluate if INB03 given as a SC injection can decrease disease progression defined as death or requirement for mechanical ventilation in participants with pulmonary complications from COVID-19 infection.

3.2 Secondary Objectives

The secondary objectives of the study are to:

- Assess the effect INB03 has on all-cause mortality in participants with pulmonary complications from COVID-19 infection;

- Determine if INB03 can decrease non-respiratory catastrophic complications of COVID-19 infection including admission to ICU, new onset neurologic, cardiovascular or thromboembolic disease, or renal failure;

- Evaluate if treatment with INB03 reduces increase in the WHO Ordinal Scale for Clinical Improvement score;

- Evaluate if length of hospital-stay in participants with pulmonary complications from COVID-19 decreases when treated with INB03;

- Evaluate the safety and tolerability of INB03 when given to participants with pulmonary complications from COVID-19 infection;

- Assess the effect INB03 has on inflammatory markers in participants with pulmonary complications from COVID-19 infection.

3.3 Exploratory Objectives

The exploratory objective of the study is to:

- Qualitatively and quantitatively evaluate the presence and nature of residual (post-Study Day 40) complaints of fatigue, malaise, affective symptoms, inflammatory cognitive dysfunction syndrome and associated functional limitations.

4 STUDY DESIGN AND ENDPOINTS

4.1 Description of the Study Design

The trial is a Phase 2, double-blind, placebo-controlled, randomized clinical trial of INB03 in participants with pulmonary complications from COVID-19 infection. Each participant will complete up to 6 study visits.

Screening: Participants with a diagnosis of COVID-19 will be screened for study eligibility. Prior to any trial related procedures, participants will provide their consent to participate in the clinical trial. Screening assessments will include:

- collection of medical history/participant demographic (including race and ethnicity);
- physical examination (including vital signs, height and weight);
- room air oxygen saturation (SaO2), if possible;
- chest imaging;
- ECG;
- WHO Ordinal Scale for Clinical Improvement (to be completed any time after informed consent is obtained and up to 1-hour post-randomization on Day 1);
- clinical laboratory evaluations (as per Table 2: Clinical Laboratory Evaluations);

- serum or urine pregnancy test for women of childbearing potential (WCBP).

If any of the above assessments are performed as part of routine clinical care within 1 day of Screening, they do not need to be repeated.

Study Day 1: Eligible participants will be randomized to receive either INB03 at 1mg/kg by subcutaneous injection (SC) + standard of care (SOC) or Placebo SC injection + SOC within 1 day of Screening. Participants will receive their first dose of study drug after randomization. Blood samples to check TNF levels and perform an anti-drug antibody test will be collected before dosing. Clinical assessments while participants are inpatients will be as per routine management of hospitalized COVID-19 patients including daily collection of vital signs, physical exam, concomitant medications and laboratory evaluations. 12-lead ECGs and chest imaging assessments will be performed if deemed clinically necessary. Additionally, use of non-mechanical ventilation will be collected daily until the participant is discharged from hospital.

The WHO Ordinal Scale will also be completed daily until the participant is discharged from hospital.

The sponsor recognizes that SOC may change over time. The study protocol allows therapies that have shown benefit in well-designed prospective randomized trials. Each clinical site can select their SOC.

Study Day 8: Participants will be given a second dose of INB03 or Placebo on Day 8 (7 days after randomization) if they remain in hospital. Clinical assessments while participants are inpatients will continue as per routine management of hospitalized COVID-19 patients and described in Table 3 – the Schedule of Assessments (SOA).

Since the timing of hospital discharge in this patient population cannot be predicted, discharge assessments will be obtained on the day the participant is to be discharged. If the participant remains in the hospital, the participant will continue with daily assessments as per Table 3 - SOA. At discharge, no additional follow-up is expected until the participant is seen for the Study Day 28 visit.

Study Day 28: A follow-up visit will be conducted on Day 28. Follow-up study assessments will include:

- physical examination (including vital signs);
- room air oxygen saturation (SaO2), if possible;
- chest imaging (if deemed clinically necessary);
- ECG;
- clinical laboratory evaluations (as per Table 2: Clinical Laboratory Evaluations);
- adverse events;
- assessment of disease progression and use of non-mechanical ventilation;
- WHO Ordinal Scale for Clinical Improvement.

If participant is still in hospital at Study Day 28, no additional follow-up is expected until the participant is seen on the Day 40 final safety visit.

Study Day 40: A final visit will be conducted on Day 40. End of study safety assessments will be conducted as per Table 3 - SOA.

Study Day 40-50: Participant will complete Long COVID questionnaires using an electronic Patient-Reported Outcomes (ePRO) portal. Assessments will include the Patient Health Questionnaire-9 (PHQ-9) and a Long COVID questionnaire (LCQ). The LCQ is a composite questionnaire that assesses Function and Performance, somatic and cognitive complaints reported to be associated with Long COVID syndrome. Additionally, the questionnaire captures life changes associated with COVID societal restrictions that existed or were anticipated prior to and *independent* of the participant's COVID-19 disease.

The Long COVID Informant questionnaire (LCIQ) will be completed by an informant, defined as someone who has known the participant for at least two years and interacts (face to face or via phone) for at least 4 hours per week beginning prior to contracting COVID-19, in person at the Study Day 40 visit or by phone. A separate informed consent form will be collected from the informant prior to completion of this questionnaire.

Study Day 50-70: In a subset of participants who report Long COVID symptoms, a telephone interview will be conducted by a third-party neuropsychologist to qualitatively and quantitatively evaluate the presence and nature of residual (post-Study Day 40) or emergent complaints of fatigue, malaise, affective symptoms, inflammatory cognitive dysfunction syndrome and associated functional limitations. This interview will consist of a semi-structured interview and open-ended questions to catalogue residual complaints which will be subjected to concept matching exercises to estimate the need for amending the LCQ to capture COVID-19 specific residuum. The interview time is estimated to be 45 minutes. Data captured during the semi-structured interviews will be de-identified and stored securely in electronic format.

Study Day 70: Participants will be contacted via telephone on Day 70 to assess AEs and changes in concomitant medications.

All laboratory, ECG, and vital signs data will be captured for data analysis and safety.

4.2 Study Endpoints

4.2.1 Primary Endpoint

The primary endpoint of the study is:

- Proportion of participants with disease progression from randomization to 28 days post-randomization, where disease progression is defined by the development of need for mechanical ventilation or death. Mechanical ventilation includes CPAP, BIPAP or mechanical ventilation requiring intubation.

4.2.2 Secondary Endpoints

The secondary endpoints of the study are:

- Proportion of participants with all-cause mortality;
- Proportion of participants who transfer to ICU level care by Day 28 (ICU level care is defined as a hospital setting where patient to nurse ratio is < 4);
- Proportion of participants with a new onset of neurologic disease (requiring medical intervention), including stroke by Day 28;
- Proportion of participants with evidence of new CHF or new MI requiring medical intervention by Day 28;
- Proportion of participants with a new onset embolus or thrombus by Day 28;
- Proportion of participants who develop a need for renal replacement therapy (defined as need for any type of dialysis including intermittent or continuous peritoneal or hemodialysis) by Day 28;
- Proportion of participants with an increase in the WHO Ordinal Scale of Clinical Improvement score at any time during the study;
- Length of hospital stay defined as the number of days in hospital from time of randomization to time of discharge or death, whichever occurs first;
- Change from baseline in inflammation markers over time.

4.2.3 Safety Endpoints

The safety endpoints of the study are:

- Incidence of adverse events and serious adverse events not due to underlying disease;
- Incidence of abnormal findings in clinical safety laboratory parameters, vital signs, and ECGs.

4.2.4 Exploratory Endpoints

The exploratory endpoints of the study are:

- Percentage of participants who report Long COVID symptoms
- Total score on the Patient Health Questionnaire-9 (PHQ-9)
- Total and subscale scores on Long COVID Questionnaire (LCQ)
- Total and subscale scores on Long COVID Informant Questionnaire (LCIQ)

4.3 Clinical Trial Committees

A Data Monitoring Committee (DMC) will be established. The DMC will assess ongoing safety at pre-specified timepoints as detailed in the DMC Charter. The DMC will also review unblinded efficacy data at the time of the interim analysis. An independent unblinded statistician who is not involved in the study conduct will provide safety and efficacy data to the DMC for review.

DMC membership, scope and frequency of safety reviews will be described in the DMC Charter.

4.4 Completion of Clinical Trial

A participant is considered to have completed the clinical trial if he/she has completed the Day 40 assessments as shown in Table 3 - SOA.

The end of the clinical trial is defined as the date of last scheduled procedure shown in the SOA for the last participant in the trial.

5 STUDY ENROLMENT AND WITHDRAWAL

5.1 Inclusion Criteria

To be eligible for study entry, participants must satisfy all of the following criteria at Screening:

1. Have one or more of the following comorbidities:
    a. Age ≥ 65 years;
    b. Obesity (BMI ≥ 30);
    c. Hypertension (on one or more drugs for treatment of hypertension);
    d. Diabetes (on one or more drugs for Type I or Type II diabetes);
    e. Cardiovascular disease (on one or more drugs for treatment of cardiovascular disease, other than aspirin);
    f. History of congestive heart failure (CHF) or myocardial infarction (MI);
    g. Black or African-American race (at least one parent identifies as Black or African-American);
    h. Hispanic or Latino ethnicity.
2. Have a positive COVID-19 test in the last 28 days;
3. Have room air SaO2 <96%, or SpO2 < 96% on room air at sea level, or PaO2/FiO2 < 300;
4. Have abnormal chest X-ray, MRI or CT scan consistent with pulmonary complications from COVID-19;
5. Provide written informed consent prior to any study related procedures being performed.

5.2 Exclusion Criteria

Participants will be excluded from the study if 1 or more of the following criteria are applicable at Screening:

1. Age < 18 years;
2. Require immediate intubation due to advanced respiratory failure – including CPAP and BIPAP;
3. Require immediate admission to an ICU for any reason;
4. On therapy with approved TNF inhibitor (eg: infliximab, etanercept, adalimumab, certolizumab pegol, golimumab, thalidomide, etc) in the last 6 months;
5. Being treated with dexamethasone (IV or PO) at a dose of >15mg per day or solumedrol or equivalent corticosteroid at a dose of >120mg per day;
6. Taking any medication known to be CCR5 receptor antagonist (eg: leronlimab, aplaviroc, vicriviroc or maraviroc) in the last 6 months;
7. Taking any medication known to inhibit the cytokine pathway (eg: anakinra, tocilizumab, siltuximab, etc) in the last 6 months;
8. Known to be pregnant;
9. Has known HIV, HCV or HBV infection;
10. Has known Mycobacterium tuberculosis infection or evidence of infection on chest X-ray;
11. Significant hepatic disease (ALT/AST> 4 times the ULN);
12. On therapy for cancer in the last 6 months;
13. On therapy for organ transplant in the last 6 months or on a waiting list for organ transplant, including patients on renal replacement therapy for any reason;
14. Known hypersensitivity to investigational product or its excipients;
15. Participating in an investigational drug or device trial;
16. Congestive heart failure (CHF) or myocardial infarction (MI) diagnosed in the last 2 months.

5.3 Reasons for Withdrawal or Termination

- A participant may withdraw from the clinical trial at any time at his/her own request.

- The investigator also has the right to withdraw the participant from the study for loss to follow-up.

The reason for study discontinuation will be recorded on the CRF.

5.4 Handling of Withdrawal or Termination

Participants withdrawing from the study will be encouraged to complete the same final evaluations as participants completing the study according to this protocol (Day 40 assessments).

Reasonable efforts will be made to contact participants who are lost to follow-up. Investigator will be expected to try as much as possible to re-connect those participants at the end of the trial in order to obtain at least their vital status. These efforts must be documented in the participant's file.

Investigators will be trained about the importance of participant retention and steps to prevent missing data.

5.5 Stopping Rules

Enrollment would be put on-hold and a DMC meeting would be convened within 48 hours if any of the following is reported:

1. Death in any participant in which the cause of death is judged to be possibly related or related to the study drug by the treating investigator;
2. The occurrence in any participant of a life-threatening SAE whose causal relationship to study drug is judged to be possibly related or related by the treating investigator;
3. Two (2) occurrences of Grade 3 or higher toxicities that are assessed to be related to the study drug by investigator;
4. Two (2) occurrences of a clinically significant Grade 3 or higher laboratory abnormality assessed to be related to the study drug by investigator.

After review of the case(s), the DMC would make a recommendation to the Sponsor concerning continuation or stopping of the trial.

Additionally, the DMC will review the safety data throughout the study and unblinded SAEs and SUSARs (not meeting criteria 1 or 2 above) will be forwarded to the DMC for review within 48 hours of the event being reported to the sponsor. The DMC may recommend at any time that the trial stop based on safety concerns.

5.6 Premature Termination or Temporary Suspension of Study

This study or the study site may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Study enrolment may be temporarily suspended if the DMC considers that the number and/or severity of adverse events justify suspension of the study. Written notification, documenting the reason for study suspension or termination will be provided by the suspending or terminating party to the investigator, and regulatory authorities.

If the study or the study site is prematurely terminated or suspended, the investigator will promptly inform the HREC/IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the HREC/IRB, or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- The investigator (or delegate) and the sponsor consider that the number and/or severity of adverse events justify discontinuation of the study;
- The Sponsor makes a unilateral request to do so.

6 INVESTIGATIONAL PRODUCTS

6.1 Treatments Administered

The clinical trial will have two treatment arms INB03 + SOC or Placebo + SOC. Approximately 183 participants will be randomized to each arm. Participants randomized to the INB03 + SOC arm will receive INB03 1mg/kg up to a maximum of 90mg. Participants randomized to the Placebo + SOC will receive a SC injection of normal saline 0.01ml/kg up to a maximum of 0.9ml.

Table 1 provides a summary of the investigational product to be administered in the study.

Table 1: Investigational Products Administered

Treatment	Dose form	Route of administration	Dose (mg)	Dose frequency
INB03	Liquid	SC injection	1mg/kg (not to exceed 90 mg)	1st dose on Study Day 1 & 2nd dose of Study Day 8 (*if participant remains in hospital*)
Placebo (Normal Saline)	Liquid	SC injection	0.01ml/kg (maximum of 0.9 ml)	

Abbreviations: SC=subcutaneous

6.2 Investigational Product Description

6.2.1 Formulation, Appearance, Packaging and Labelling

INB03

INB03 is a pegylated protein variant of sTNF, originally developed by Xencor Inc (United States Investigation New Drug 100,130) under the name XPro™ 1595. Refer to the INB03 IB for additional formulation and manufacturing specifics.

INB03 drug product is a liquid product supplied in single-use glass vials in a dose strength of 110 mg of drug. A 1.1 mL volume of drug product contains 100 mg/ml of INB03 and the following inactive ingredients: histidine, sodium chloride, and polysorbate 20 at pH 6.5.

The 100 mg/mL product vial is intended to deliver 1.0 mL of drug solution or 100 mg of INB03.

INB03 vials will be stored, labelled and distributed to the pharmacy of each study site by the Central Pharmacy. Prior to administration, INB03 will be prepared in syringes for SC injections as detailed in the Pharmacy Manual. The syringes will be labelled by pharmacy to maintain the blind.

Placebo

Placebo will be normal saline from the site pharmacy's stock. Saline is a clear liquid comparable in appearance to INB03. Prior to administration, Placebo will be prepared in syringes for SC injections as detailed in the Pharmacy Manual. The syringes will be labelled by pharmacy to maintain the blind.

6.2.2 Storage and Stability

INB03 should be stored in a refrigerator between 2 to 8 ºC and be removed from the refrigerator at least 15 to 30 minutes prior to administration in order to reach room temperature. INB03 should not be mixed or diluted with other drugs or solutions, and it should be administered within 8 hours of preparation in syringes for SC injection. Prepared syringes can remain in room temperature until administration. Any unused study drug in syringes must be discarded.

Placebo (normal saline) will be stored as per the manufacturer's recommendation.

6.3 Dosing and Administration

All randomized participants will receive either INB03 1mg/kg (not to exceed 90 mg) by SC injection or Placebo by SC injection immediately upon randomization (Study Day 1). A second dose of study drug will be administered on Study Day 8, if participant remains in hospital.

6.4 Blinding and Randomisation

6.4.1 Blinding

Study drug (INB03 or Placebo) will be provided in identically appearing syringes. The syringes will be prepared and labelled by the unblinded pharmacist prior to dispensing in order to maintain the blind.

6.4.2 Un-blinding

While unblinding is highly discouraged, if it is deemed necessary to unblind a participant's treatment in order to provide medical management of an adverse event or to provide emergency treatment, the site should aim to contact the Medical Monitor to discuss the case and reason for unblinding. However, if the site cannot reach the Medical Monitor, they should contact the

unblinded pharmacist to break the blind and obtain treatment information. The site should then notify the Medical Monitor as soon as possible. Procedure for un-blinding will be detailed in the Pharmacy Manual.

Unblinding should only occur if necessary for the medical management of the participant. Participants who are unblinded will be terminated from study treatment, but safety follow-up will continue.

6.4.3 Randomisation

Participants will be randomized 1:1 on Study Day 1 in a blinded fashion to either treatment with INB03 or Placebo. Due to the complexity of COVID-19 and need for immediate randomization, each site pharmacist will be provided with a randomization schedule unique to the specific site. Separate randomization schedules will be generated for each site participating in the trial. The same criteria for generation of the list will be used for each site (e.g., block size, list structure) but lists will be unique for each site. The pharmacist at each site will be unblinded and will be responsible for providing the randomization number to site personnel.

An independent unblinded statistical team will generate each unblinded randomization schedule and will provide each list directly to the site pharmacist in a secure manner.

Full details of the randomization process, roles and responsibilities, will be described in the Pharmacy Manual.

6.4.4 Storage of Supplies

Study materials will be stored by the study personnel according to the documentation provided with the study materials. The sponsor reserves the right to inspect the investigational product storage area before and during the study. A written record will be made of the storage condition of the study materials and retained for the Investigator Site File.

6.4.5 Dispensing and Accountability of Investigational Product

The investigator is responsible for the investigational product accountability, reconciliation and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the investigator or designated site staff must maintain investigational product accountability records throughout the course of the study. The amount of investigational product received from the sponsor or from pharmacy stock (for normal saline), the amount supplied and/or administered to participants will be documented. Accounts of any investigational product accidentally or deliberately destroyed will also be maintained. It will be the responsibility of the sponsor to ensure that adequate samples of all study doses are retained in accordance with the relevant regulatory guidelines.

Dispensing of the investigational product will be carefully recorded on appropriate investigational product accountability forms and will be verified by the unblinded study monitor during monitoring visits.

The accountability logs should include dates, quantities, batch numbers, expiration dates (if applicable), and any unique pack numbers assigned to the investigational product and/or participant. The accountability logs will also include general details related to the study including the protocol/amendment number, sponsor and the investigator.

Given that study drug syringes will be in close proximity to COVID-19 participants, the site will need to follow their standard operating procedures on the destruction of used syringes, including immediate destruction after use. In this case, the unblinded study monitor will review the investigational product accountability logs and check all investigational product dispensed by pharmacy against the hospital record medical chart. Unused pharmacy stock will also be reviewed by the unblinded study monitor.

6.5 Contraception

The effects of INB03 on fetal development have not been ascertained. As such, all WCBP and men whose sexual partner(s) is/are WCPB must agree to use an acceptable, highly effective method of contraception from the time of enrolment until 30 days after the last dose of study drug. Acceptable, highly effective forms of contraception includes:

- oral contraception;
- intrauterine device;
- systemic (injectable or patch) contraception;
- double barrier methods;
- naturally or surgically sterile;
- strict abstinence or
- partner has been sterilized.

6.6 Concomitant Medications

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of screening or receives during the study until discharge from the hospital must be recorded on the CRF along with:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency

Additionally, at the Study Day 28 and Day 40 visits, any changes to concomitant medications since the last study visit will be recorded.

If the use of any concomitant treatment becomes necessary (eg, for treatment of an AE), the treatment and administration details must be recorded in the source documents and the CRF. The

medical monitor must be notified of all prohibited medications administered to any participant, in order to assess the participant's eligibility to continue in the study.

6.6.1 Prohibited Medications

The following medications are prohibited during the study:

- Dexamethasone (IV or PO) at a dose of >15mg per day;
- Solumedrol or equivalent corticosteroid at a dose of >120mg per day;
- TNF inhibitors (eg: infliximab, etanercept, adalimumab, certolizumab pegol, golimumab, thalidomide);
- CCR5 receptor antagonist (eg: leronlimab, aplaviroc, vicriviroc or maraviroc);
- Cytokine pathway inhibitors (eg: anakinra, tocilizumab, siltuximab)

7 STUDY ASSESSMENTS AND SCHEDULES

7.1 Safety Assessments

Refer to the Schedule of Assessments (Table 3) for the timing of all safety assessments.

7.1.1 Medical History

Relevant medical history will be collected at Screening and will include evaluation for cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, metabolic, lymphatic, hematologic, immunologic, dermatologic, psychiatric, and genitourinary disorders, medication, smoking and surgical history.

7.1.2 Physical Examination

The physical examination will be as per standard of care. The details of the examination will not be captured on the case report form (CRF). However, any clinically significant findings should be captured as an AE.

7.1.3 Body Weight and Height

Body weight (in kg) (wearing light clothes, no shoes) and height (in cm) will be measured.

7.1.4 Chest Imaging

Lung imaging studies (X-ray, MRI or CT) will be performed upon hospital admission to confirm pulmonary disease due to COVID-19. The investigational site may repeat the imaging studies as per SOC while the participant is an inpatient.

7.1.5 12-lead Electrocardiogram

A 12-lead ECGs will be performed as per the investigational site's SOC and routine assessment provided. The investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

ECGs will be performed, at a minimum, at the time of Screening, at Study Day 28 and at Study Day 40. Data for all routine ECGs performed while the participant is an inpatient will be captured on the CRF.

7.1.6 Vital Signs

Vital signs measurements will include body temperature, respiratory rate, heart rate and systolic and diastolic blood pressure. The vital signs should be taken at approximately the same time each day, preferably between 12pm-5pm.

7.1.7 Clinical Laboratory Safety Tests

Blood samples (up to 25 mL) will be collected for clinical laboratory safety tests at the timepoints specified in Table 3 - SOA. A list of laboratory evaluations is provided in Table 2: Clinical Laboratory Evaluations below.

Table 2: Clinical Laboratory Evaluations

Haematology	Hematocrit Hemoglobin Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count Red blood cell (RBC) count RBC distribution width	White blood cell (WBC) count WBC differential (absolute): Basophils Eosinophils Lymphocytes Monocytes Neutrophils
Clinical Chemistry	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Aspartate aminotransferase (AST) Calcium Carbon Dioxide (CO_2) Chloride Creatinine	Creatinine phosphokinase Glucose Phosphorus Potassium Sodium Total bilirubin Total protein
COVID-19 Specific	eGFR Troponin CRP Ferritin D-dimer	*At a minimum will be collected:* • *Screening Visit* • *Every 2 days during hospitalization* • *Discharge Visit* • *Day 28 Visit* • *Day 40 Visit*
Other	Pregnancy Test (urine or serum)	*To be performed for WCBP at Screening Visit*
	Tumour Necrosis Factor (TNF)	*To be collected:* • *Day 1 (**before dosing with study drug**)*
	Anti-drug Antibody (ADA)	*To be collected:* • *Day 1 (**before dosing with study drug**)* • *Day 28 Visit* • *Day 40 Visit*

If laboratory evaluations are performed more than once a day as part of the routine management of hospitalized COVID-19 patients, the results from the first set of daily labs collected will be reviewed for this study and entered in the CRF.

Safety clinical laboratory samples will be analysed by the investigational site's local pathology laboratory.

The ADA test will be collected by the site and sent to the central laboratory for analysis. Instructions on collection, processing and preparation for shipment of central laboratory samples will be provided in the Central Laboratory Manual.

7.1.8 Use of Non-mechanical Ventilation

Participants will be assessed daily for use of non-mechanical ventilation until discharge from hospital, at Study Day 28, and Study Day 40. Details on type of non-mechanical ventilation used will be captured on the CRF as well as max fractioned of inspired oxygen (FiO2) used and SaO2 achieved.

7.1.9 Adverse Events

7.1.9.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study participant administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the CRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

7.1.9.2 Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening (i.e., the participant is at immediate risk of death at the time the event occurred; it does not refer to an event which might hypothetically have caused death had it been more severe);
- Requires in-patient hospitalisation or prolongation of existing hospitalisation. Since hospitalization is part of the clinical trial, only hospitalizations that are longer than expected for the clinical management of COVID-19 patients, based on Investigator judgment, will be considered prolonged hospitalizations.

- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is a medically important event or reaction: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

7.1.9.3 Severity of Adverse Events

The investigator will make an assessment of intensity for each AE and SAE reported during the study. All AEs and SAEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (CTCAE Quick Reference Guide). Grade refers to the severity of the AE and the CTCAE displays Grades 1 through 5, as applicable to the AE.

7.1.9.4 Relationship of Adverse Events to Investigational Products

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

The causal relationship of the AE to the investigational product or study procedures should be assessed by the investigator (or medically qualified delegate) using the following classifications:

Not Related	In the investigator's opinion, there is not a causal relationship between the study product and the AE.
Possibly Related	The AE follows a reasonable temporal sequence from the time of study product administration but could have been caused by the participant's clinical state or other modes of therapy administered to the participant.
Related	The AE follows a reasonable temporal sequence from the time of study product administration, abates upon discontinuation of the study product and reappears when study product is reintroduced.

7.1.9.5 Recording of Adverse Events

Adverse Events will be recorded and reported from the study enrolment until Study Day 70 for all participants who are randomized. Refer to Section 7.1.9.1 for definition of AEs.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostic reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in to the CRF. All

details of any treatments initiated due to the AE should also be recorded in the participants' notes and the CRF.

Each AE will be documented in the participant's CRF. If an AE changes in frequency or intensity during a study, a new entry of the event must be made in the CRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms should be documented.

All AEs occurring during the study must be documented on the relevant CRF pages. The following data should be documented for each AE:

- Description of the symptom event;
- Classification of 'serious' or 'not serious';
- Severity - graded according to the CTCAE v5.0;
- Date of first occurrence and date of resolution (if applicable);
- Action taken;
- Causal relationship;
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death) [with date and cause reported].

After the initial AE or SAE report, the investigator is required to proactively follow each participant and provide further information to the sponsor on the participant's condition.

All AEs are required to be assessed by a medical practitioner. All AEs or SAEs documented at a previous visit/contact that are designated as ongoing, will be reviewed at subsequent visits/contacts. All AEs or SAEs assessed as related to IP will be followed until Study Day 70. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE.

The follow-up safety assessments conducted at Study Day 40 and Study Day 70 will allow for safety data to be captured at 30 and 60 days after the last dose of study drug, respectively. The post-treatment safety follow-up will be used to determine if an observed AE or SAE assessed as related to IP has either resolved, returned to baseline status, or has been adequately investigated and assessed by the investigator as chronic and/or stable. Additionally, the investigator will confirm that no long-term adverse effects have become evident during the post-treatment safety follow-up period.

7.1.9.6 Reporting of Serious Adverse Events

As the sponsor has a legal responsibility to notify the appropriate regulatory authorities about the safety of a new test drug, prompt notification by the investigator, or nominee, of any SAEs to the sponsor is required.

All SAEs, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor within 24 hours of site awareness.

In addition to reporting the SAE to sponsor, the investigator must also notify the HREC which approved the study according to their requirements.

Copies of all correspondence relating to reporting of any SAEs should be maintained in the site's study files and will be checked routinely by the Study Monitor.

If the sponsor and the investigator consider that the SAE is investigational product related (ie, an adverse reaction) and unexpected it will be reported to the appropriate regulatory authorities by the sponsor (or designee) within the pre-defined timelines.

7.2 Efficacy Assessments

Refer to the Schedule of Assessments (Table 3) for the timing of all efficacy assessments.

7.2.1 Disease Progression

Participants will be assessed from randomization to 40 days post-randomization for development of disease progression defined as:

- **Need for mechanical respirator support:** If a participant has progressed from passive oxygen support (nasal canula, face mask, etc) to needing something that is attached to an active device/machine (eg: CPAP), this is considered as needing mechanical respirator support.
- **Death:** Time, date and cause of death should be recorded.

Additionally, participants will be assessed for the following non-respiratory complications of COVID-19 from randomization to Day 40:

- **Transfer to ICU level care:** In the midst of a surge, the definition of an ICU may be stretched to include cardiac care unit (CCU), step-down unit or any place that has been set up to receive patients that may need mechanical ventilation. ICU level care is defined as a hospital setting where patient to nurse ratio is ≤ 4.
- **New onset myocardial infarction (MI) or congestive heart failure (CHF):** the development of CHF or MI once enrolled in the study is made by standard clinical/laboratory/imaging modalities based on the best judgement of the clinical team. The development of congestive heart failure or new myocardial infarction will often initiate some sort of medical intervention.

- **Requirement for renal replacement therapy:** The decision to initiate renal replacement therapy is made by the clinical team. Renal replacement therapy means any form of dialysis including intermittent or continuous peritoneal or hemodialysis.
- **New onset neurologic symptoms:** Any neuropsychiatric symptom that requires medical intervention qualifies. This can be, but is not limited to, stroke, encephalopathy, seizures, hallucination and coma. Neuropsychiatric symptoms caused by hypoxia or hypotension are not considered a COVID-19 related neurologic symptom.
- **New onset thrombotic or embolic event:** The development of venous or arterial thrombosis or embolus that requires medical intervention that occurs after enrollment is new onset. Thrombosis of peripheral or central venous access, arterial lines or dialysis catheters is not considered a thromboembolic event endpoint.

7.2.2 WHO Ordinal Scale for Clinical Improvement

The Ordinal Scale for Clinical Improvement is from the WHO R&D Blueprint designed for use in the COVID-19 population to measure illness severity over time. The scale will be completed for all participants at Screening (any time after consent is obtained and up to 1-hour post-randomization at Day 1). Daily assessments will be conducted using the Ordinal Scale for Clinical Improvement while participants are inpatients during the afternoon hospital rounds until participants are discharged from hospital.

The scale will also be completed at the time of hospital discharge, at the Day 28 follow-up visit and a final assessment with the Ordinal Scale for Clinical Improvement will be conducted on the Day 40 final safety visit.

7.3 Exploratory Assessments

Exploratory assessments will include both quantitative and qualitative variables.

7.3.1 Quantitative Variables

Patient Health Quesitonnaire-9 Item version (PHQ-9) is a self-administered rating scale designed to screen for the presence and frequency of depressive symptoms with a total score range of 0 to 27 and item ratings reflecting 4 severity levels with “0” meaning “Not at all” to 3 to denote “nearly every day.”

Long COVID Questionnaire (LCQ) is a self-administered questionnaire to be completed by each study participant on Study Day 40 or between Days 40 and 50 in an electronic format (ePRO). It consists of three subscales composed of items captured from informal online surveys from Long COVID complainants (16 items, rated on a 4 point scale relative to pre-COVID health) as well as selected items adapted from two ratings scales developed for use in dementia and traumatic brain injury respectively (eCog and PAOFI) to capture subjective experience of functional (17 items rated on a 4-point scale) and cognitive changes (9 items rated on a 6-point scale) relative to pre-

COVID functioning. Lastly, the questionnaire captures changes in life circumstances extrinsic to participant COVID-19 disease. For example, related changes in personal finances associated with loss of employment (or enhanced employment opportunity), changes in home life, impact on life plan (i.e. in retirement) that were present or imminent for the study participant prior to COVID-19 disease onset. These variables may be used as covariates if there is a random imbalance between treatment groups on the frequency and direction of these life events.

Long COVID Informant Questionnaire (LCIQ) is a self-administered questionnaire containing 17 items selected from the eCog that have been adapted for Long COVID and reflects an informant's perspective on changes in life functioning temporally associated with COVID-19 disease onset. Items are rated on a 4-point scale. This questionnaire will be completed in person if the informant accompanies the participant on the Study Day 40 visit. Otherwise, the study coordinator will contact the informant between Days 40-50 and complete the questionnaire via the telephone.

7.3.2 Qualitative Measure

Qualitative research methods consistent with those outlined in the FDA draft guidance "Patient-Focused Drug Development: Methods to Identify What is Important to Patients" will be employed in conducting and analysing participant interview data. Semi-structured interviews with some open-ended questions will be conducted in a subset of those participants who present with Long COVID syndrome. Narrative responses will be coded by identifying and classifying distinct concepts and proceeding with interviews until concept saturation is achieved. This effort is designed to assure that the above questionnaires have adequately captured Long COVID syndrome, and if not, to inform enhancements to these questionnaires for subsequent trials.

8 STUDY SCHEDULE OF ASSESSMENTS

The Schedule of Assessments is provided in Table 3.

Table 3: Schedule of Assessments

		All tests after Day 1 and up to Day 27 only performed until participant is discharged from hospital or Study Day 27, whichever occurs first *= only performed if clinically indicated																													
Visit Windows (Days)	**Screening[1]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**Discharge**	**28[2]** (+3d)	**40[2]** (±2d)	**70** (±2d)
Informed Consent	X																														
Inclusion/ Exclusion Criteria	X																														
Participant Demographics	X																														
Medical History	X																														
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight/Height	X																														
Concomitant Meds[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Room Air SaO2	X																												X	X	
Chest Imaging	X	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	
12-lead ECG[4]	X	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	X	X	
COVID-19 test[5]	X																														
Chemistry[6]	X	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	X	X	X	
Haematology[6]	X	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	X	X	X	
COVID-19 Labs[6]	X	*	X	*	X	*	X	*	X	*	X	*	X	*	X	*	X	*	X	*	X	*	X	*	X	*	X	*	X	X	X	
Pregnancy Test[7]	X																														
TNF Blood Level[6,8]		X																													

		All tests after Day 1 and up to Day 27 only performed until participant is discharged from hospital or Study Day 27, whichever occurs first *= only performed if clinically indicated																													
Visit Windows (Days)	**Screening[1]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**Discharge**	**28[2]** (+3d)	**40[2]** (±2d)	**70** (±2d)
Anti-drug Antibody[9]		X																												X	X	
Randomization		X																														
Study Drug Administration		X							X[10]																							
WHO Ordinal Scale[11]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Disease Progression			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Non-mechanical Ventilation Use		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Reporting[13]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Long COVID Questionnaires																															X[14]	

Abbreviations: AE = Adverse Event, ECG = electrocardiogram, MRI = magnetic resonance imaging.

1. Can be same as Day 1.

2. Every attempt should be made to conduct the Day 28 Visit (+3d) and the Day 40 Visit (±2d) on site to ensure collection of all study safety assessments. Remote conduct of the Day 28 and Day 40 Visits (i.e. via Telehealth) will be considered by the sponsor on a case by case basis.

3. The vital signs should be taken at approximately the same time each day, preferably between 12pm-5pm.

4. Data for all routine 12-lead ECGs performed while the participant is an inpatient will be captured on the CRF. Additionally, the Day 28 and Day 40 12-lead ECG can be omitted if this visit is conducted remotely.

5. Testing for COVID-19 needs to have been performed and a positive result obtained within 28 days of Screening.

6. If laboratory evaluations are performed more than once a day as part of the routine management of hospitalized COVID-19 patients, the results from the first set of daily labs collected will be reviewed for this study and entered in the CRF. Safety clinical laboratory samples will be analysed by the investigational site's local pathology laboratory.

7. Pregnancy test (urine or serum) will be performed for women of childbearing potential at screening.

8. Blood sample to check TNF levels will be collected prior to dosing with study drug on Day 1. This lab will be analysed at the investigational site's local pathology laboratory.

9. Blood sample to perform anti-drug antibody (ADA) test will be collected prior to dosing with study drug on Day 1. ADA samples will also be collected at Day 28 and Day 40. This lab will be collected at the site and shipped to the central laboratory for analysis.

10. The second dose of study drug will be administered on Day 8, if participant is still in hospital.

11. The Screening WHO Ordinal Scale will be completed any time after informed consent and up to 1-hour post-randomization on Day 1. The scale will then be completed daily during the afternoon hospital rounds until participants are discharged from hospital. The scale will also be collected on Day 28 and Day 40.

12. Participants will be assessed for development of disease progression from randomization to Study Day 40.

13. Concomitant medications and AEs will be recorded for all participants who are randomized until Study Day 70.

14. Participants may complete Long COVID questionnaires via ePRO (participants) or paper pencil (informants) between Study Day 40-50.

9 STATISTICAL METHODS

9.1 Determination of Sample Size

A total sample size of 366 participants randomized 1:1 to treatment with either INB03 + SOC or Placebo + SOC (N=183 in each arm) will provide adequate power to compare the proportion of participants with disease progression in each group by Day 28. It is assumed that 21% of enrolled participants randomized to Placebo + SOC will progress whereas the expected disease progression rate will be reduced by two-thirds to 7% in participants randomized to INB03 + SOC. To observe the expected treatment effect, N=346 (N=173 per arm) are required.

Additionally, an interim analysis for futility will be performed when approximately 20% of participants required to observe the expected treatment effect complete the Study Day 28 visit (N~70). Participants evaluated in the interim analysis include those who are randomized and receive study drug and have the Day 28 assessment or who had an intercurrent event prior to Day 28. Imputation of missing data will be performed as described in Section 9.5.1. A custom Z-statistic boundary will be used to assess futility.

The proposed study with the above assumptions will have at least 90% power assuming a one-sided Z-Test with α=0.005.

9.2 Statistical and Analytical Plans

Details of statistical parameters and methods to be used will be described in a Statistical Analysis Plan (SAP). The SAP will be developed and finalized prior to database lock and unblinding. The SAP will describe details regarding the statistical methodology to assess differences between treatment groups, all data handling procedures and definitions, including further details on the methods used for managing missing data.

9.3 Analysis Populations

The analysis populations are as follows:

9.3.1 Intent-to-treat (ITT)

All participants who have signed informed consent, meet inclusion/exclusion criteria, are enrolled in the study and who are randomized to a treatment arm will be included in the ITT population. The ITT will be the analysis population for disposition and demographic reporting purposes. Analyses will be based on the randomized treatment.

9.3.2 Modified Intent-to-treat (mITT)

The modified ITT population is a subset of the ITT population and includes participants who have received any amount of INB03 or Placebo. The mITT will be the primary analysis population for all efficacy reporting purposes. Analyses will be based on the randomized treatment.

9.3.3 Per-Protocol Set (PPS)

All participants included in the ITT population with no major protocol deviation will comprise the PPS. The PPS will be a secondary analysis population for select efficacy endpoints. Analyses will be based on treatment received.

9.3.4 Safety Set (SS)

All participants who have received any amount of INB03 or Placebo are included in the safety set. The SS will be the analysis set for safety reporting and will be based on treatment received (INB03 or Placebo).

9.4 Statistical Methods

Statistical analyses will be performed using SAS 9.4 or higher. In general, continuous variables will be summarized using number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be tabulated with frequency counts and percentages. All summary tables will be presented by treatment arm. Where appropriate, 95% confidence intervals (CIs) will be provided. All data will be listed.

Hypothesis testing of the primary efficacy endpoint will be performed based on a one-sided test with $\alpha=0.005$

Any changes in the protocol planned analyses will be described and documented in the SAP and/or clinical study report.

9.5 Efficacy Endpoints

Statistical analysis for the primary efficacy endpoint will be performed with a one-sided $\alpha=0.005$ level of significance. Secondary endpoints will also be analyzed, however no adjustment for multiplicity is planned for the secondary endpoints. Therefore, nominal p-values will be provided for the secondary efficacy endpoints. Analyses and summary statistics will be based on the mITT population. Sensitivity and other supplemental analyses may be repeated in other analysis populations.

9.5.1 Primary Endpoint

The primary estimand will be estimated based on the mITT population and includes randomized participants who have been diagnosed with COVID-19, have at least one co-morbidity, are admitted to the hospital and have pulmonary complications due to COVID-19 who receive any amount of study drug. To estimate this estimand, all post-randomization data up until Day 28 of the study will be used in the evaluation of treatment difference regarding disease progression. The estimator is the proportion of participants with disease progression up until Day 28 post-randomization where disease progression defined as is administration of mechanical ventilation or death.

As specific intercurrent events may occur that could lead to missing or spurious data, the following strategies will be used.

- Participant withdraws consent and has missing disease progression data: The "Treatment Policy" strategy for this event will be employed. The last available post-randomization record of the WHO Ordinal Scale for Clinical Improvement will be used to identify disease progression. If mechanical ventilation or death data are missing from the database, and if the last available post-randomization score is 7 or greater, the participant will be considered to have disease progression for the primary analysis of the primary endpoint.

- Participant is lost to follow-up and have no hospital discharge date and data regarding disease progression is missing: The "Composite" strategy for this event will be used. Participants with this intercurrent event are considered to have disease progression. This strategy assumes participants who remain in the hospital but are lost to follow-up for any reason are assumed to have disease progression. Similarly, participants who are discharged from the hospital and do not have information collected up to Day 28 are assumed to have disease progression.

- Participant is lost to follow-up and has a hospital discharge date and data regarding disease progression is missing: The "Treatment Policy" strategy for this event will be employed. The last available post-randomization record of the WHO Ordinal Scale for Clinical Improvement will be used to identify disease progression. If mechanical ventilation or death data are missing from the database, and if the last available post-randomization score is 7 or greater, the participant will be considered to have disease progression for the primary analysis of the primary endpoint.

- In the rare circumstance where a participant who is not lost to follow-up and did not withdraw consent and whose data regarding disease progression is missing: The "Treatment Policy" strategy for this event will employed. As disease progression is also collected through the WHO Ordinal Scale for Clinical Improvement, if mechanical ventilation or death data are missing from the database, the last post-randomization record of WHO Ordinal Scale for Clinical Improvement will be used to support the disease progression endpoint. If a score of 7 or higher is recorded, the participant will be considered to have disease progression for the primary analysis of the primary endpoint.

All participants will have a binary value or 0 or 1, where:

0=No disease progression
1=Disease progression

Descriptive statistics will be presented for the number and percent of participants with disease progression by Day 28.

The analysis method used to compare treatment groups INB03 + SOC and Placebo + SOC will be a stratified Cochran-Mantel-Haenszel (CMH) test. Stratification factors of Age (≤50, >50 to 65, >65) and number of co-morbidities (1, 2, 3+) will be included to compare the response rate of INB03 + SOC to Placebo + SOC. Treatment differences will be compared using α=0.005 one-

sided significance level and odds ratios (ratio of odds in INB03 + SOC arm to the odds in Placebo + SOC only arm) and the 95% confidence interval will be provided. If expected, cells counts are not sufficient for each strata, strata levels may be combined for the analysis.

9.5.1.1 Supportive Analysis

A supportive analysis will be performed on the primary estimand using a logistic regression analysis model with treatment group and continuous covariates of age at baseline and number of co-morbidities at baseline included in the model as covariates. Parameter estimates and the corresponding 95% CIs will be provided.

9.5.1.2 Sensitivity Analysis

Alternative methods for handling of intercurrent events will include the following:

- Participants who withdraw consent and have missing disease progression data: The "Composite" strategy will be used. Participants will be considered as having disease progression.

- Participants who withdraw consent and have missing disease progression data: Participants randomized to Placebo will use the "While on Treatment" strategy for this event as described for the primary estimand and participants randomized to INB03 will use the "Composite" strategy.

A tipping point analysis allowing the handling of missing data in the two study arms to vary independently to determine thresholds where there is no longer evidence of a difference in the primary endpoint will be conducted.

Additional sensitivity analyses may be defined in the SAP.

9.5.1.3 Supplementary Analysis

Supplemental analyses will be performed on different populations as defined for the primary estimand (Section 9.5.1). The estimation methods and estimator of the supplemental analysis estimands are the same as the primary estimand and the statistical analysis methods as described in Section 9.5.1 will be conducted on each supplemental analysis estimand.

- Population: Participants in the ITT population.
    - Intercurrent event: Participants who are randomized who do not receive study treatment – The "Treatment Policy" strategy will be used for these events. Participants will be assessed for the estimator as if they received study drug.
    - Further intercurrent events as defined for the primary estimand will be followed for this sensitivity analysis.
- Population: Participants in the PPS population.

Additional analyses may be described in the SAP.

9.5.2 Secondary Endpoints

Descriptive statistics will be provided for each secondary endpoint and reported by treatment group. Absolute values and changes in inflammatory markers as well as the WHO Ordinal Scale for Clinical Improvement collected each day in hospital will be presented by day and treatment group. Length of stay in index hospital will also be descriptively summarized. The number and percent of participants with the following will be summarized by treatment group:

- Have a 1 point, 2 point etc. increase/decrease in WHO Ordinal Scale
- All-cause mortality at any time within Day 28 visit
- Transfer to ICU level care within Day 28 visit
- Have a new onset of neurological disease within Day 28 visit
- Have evidence of new CHF or new MI requiring medical intervention within Day 28 visit
- Have new onset of embolus or thrombus within Day 28 visit
- Develop need for renal replacement therapy within Day 28 visit

Graphical presentation of endpoint data may be presented and will be described in the SAP.

The secondary estimand population for all secondary endpoints will be estimated based on the mITT population and includes randomized participants who have been diagnosed with COVID-19, have at least one co-morbidity, are admitted to the hospital and have pulmonary complications due to COVID-19 who receive any amount of study drug. To estimate this estimand, all post-randomization data up until Day 28 of the study will be used in the evaluation of each secondary endpoint. Specific handling of intercurrent events for each secondary estimand will be defined in the SAP.

The statistical analyses for secondary estimators with binary outcomes will be performed using CMH tests similar to the primary estimator. In addition, logistic regression analyses as described for the primary efficacy estimator may be performed. Treatment arm will be included in the model as well as age and number of co-morbidities at baseline as covariates. Parameter estimates, odds ratio and the corresponding 2-sided 95% CIs will be provided.

The statistical analysis model for secondary estimators with continuous outcomes will use an analysis of covariance (ANCOVA) or mixed model-repeated measures (MMRM), when assessments are repeated over time, with treatment and age and number of co-morbidities at baseline included as covariates. For MMRM analyses, visit will also be included in the model. The baseline value for change from baseline endpoints will also be included as a variable in the model. Least-square means will be provided for the treatment differences (INB03+SOC vs Placebo + SOC) as well as the corresponding 95% CIs.

9.5.3 Subgroup Analyses

Subgroups may be explored; details will be included in the SAP.

9.5.4 Safety Endpoints

Current standard of care includes assessing vital signs daily and on an as needed basis, clinical laboratory blood collection and ECG assessments. At time of index hospital discharge, laboratory, vital signs and other safety measures as defined on the Schedule of Assessments (Table 3) will be collected. Non-disease related adverse events will be collected until Day 70.

All safety summaries will be provided for the safety set.

9.5.4.1 Adverse Events

Non-disease related AEs will be coded using the MedDRA classification system. Relationship to study drug will be assessed by the investigator and reported on the CRF. Reported AEs, SAEs and related AEs will be summarized by treatment arm and overall and by system organ class (SOC) and by preferred term.

9.5.4.2 Vital Signs, Electrocardiogram and Laboratory Assessments

Vital signs and laboratory tests will be summarized as absolute values and change from baseline by treatment arm. Participants with fever (≥38^{o}C) and days with fever will be tabulated. Baseline is defined as the latest value in the database prior to randomization. Listings of abnormal laboratory parameter results will be provided.

Electrocardiogram data collected throughout the study period will be provided in data listings.

9.6 Other Analyses

9.6.1 Demographics and Baseline Characteristics

Participant demographics and baseline co-morbidities will be collected at screening and summarized by treatment arm and overall.

The date of COVID-19 confirmed case will also be collected. Further data to be collected includes date and time of admission to hospital and date participant first knew they had a fever.

9.6.2 Prior and Concomitant Medications

Prior medication collection will be limited to medications required for review of entry criteria. Medications participant is currently taking as well as new medications prescribed while on study will be collected in the CRF. All medications will be coded according to the World Health Organization (WHO) Drug Dictionary and provided in patient listings.

9.6.3 SaO2

Absolute values and changes at each timepoint of collection will be reported. Baseline is defined as the latest value in the database prior to randomization. All data will be included in patient listings.

9.6.4 Other Efficacy Assessments

Chest imaging may be performed throughout the study as deemed necessary by the investigator to assess COVID-19 disease. Imaging details will be provided in a listing.

Participants are to complete the LCQ and the PHQ-9 on Day 40-50. The percentage of participants who complete the LCQ and PHQ-9 will be reported. The total and subscale scores from the LCQ and total score from the PHQ-9 will be summarized descriptively and reported by treatment group. Similarly, the total and subscale scores from the LCIQ will be summarized.

9.7 Analysis and Reporting

9.7.1 Interim Analyses

An interim analysis will be performed when approximately 70 participants in the mITT population have completed the Study Day 28 assessment or who have an intercurrent event within 28 days on study (withdrawal or lost to follow-up). Imputation of missing data will be performed as described in Section 9.5.1.

Efficacy data, including the primary endpoint and cumulative safety data will be reviewed at the time of the interim analysis by the DMC.

A non-binding one-way futility analysis will be performed. The futility boundaries were derived using custom Z-statistic. The Z-statistic chosen as the boundary is considered clinically relevant and has a high probability of success at the final analysis with conditional power of at least 81.5%. At the time of the interim analysis, the Z-statistic boundary was chosen based on a 7.5% treatment difference corresponding to a placebo event rate of 20% and INB03 event rate of 12.5%. The futility boundary will be set at $Z<-0.8505$ (one-sided test). Should the result of the primary endpoint analysis Z-statistic be greater than -0.8505 (one-sided p-value ≥ 0.1975), the futility boundary will be considered crossed, and futility assumed. At the time of interim analysis, the boundary may be recalculated based on true number of participants with evaluable data included in the interim analysis population.

In order to maintain the study blind, an independent unblinded statistical team not involved in the conduct of the study will perform the analyses and present the results to the DMC during a closed meeting where only the DMC members and the unblinded statistician attend.

A preliminary analysis of the primary efficacy data will be performed prior to the final database lock. The primary efficacy endpoint will be analyzed and a limited number of individuals who are not involved in the study conduct or review of day-to-day activities of the study will be informed on the unblinded efficacy results in order to plan further development and inform on other corporate objectives. The DMC will also review unblinded safety and the primary efficacy data and recommend to the sponsor their unbiased opinion concerning safety and efficacy of INB03 in an acute COVID population.

The futility analysis is non-binding and the DMC will make a recommendation based on review of primary efficacy and safety data. The DMC will recommend the trial continue as planned or be terminated due to futility or safety concerns. There will be no early termination due to positive efficacy signals.

The decision to terminate the trial will be at the sole discretion of the sponsor.

9.7.2 Final Analysis

The final analysis will occur once all participants complete their end of study visit or their last scheduled assessment per the Schedule of Assessments (Table 3), or the sponsor terminates the study for any reason.

10 STUDY DOCUMENTATION

10.1 Access to Source Documents

In compliance with local regulations and ICH GCP guidelines, it is required that the investigator and institution permit authorised representatives of the sponsor, the regulatory agency(s), and the HREC/IRB direct access to review participants' original medical records for verification of study-related procedures and data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform the participant and obtain their consent to permit named representatives to have access to his/her study-related records without violating the confidentiality of the participant.

10.2 Protocol Amendments

No changes (amendments) to the protocol may be implemented without prior approval from the sponsor and the appropriate HREC/IRB, except where necessary to eliminate an immediate hazard to participants. If a protocol amendment requires changes to the Participant Information and Consent Form/Informed Consent Form (PICF/ICF), the revised PICF/ICF must be approved by the HREC/IRB.

10.3 Protocol Deviations

If any issue relating to the safety of the participant arises which requires a deviation from the protocol, the study unit through the investigator may immediately make such a deviation (protocol breach). If there is a need for such a deviation, the study unit must notify the sponsor and the responsible HREC/IRB of the facts and circumstance causing the deviation. Protocol deviations that occur specifically due to the COVID-19 outbreak will be clearly coded as such.

Serious protocol breaches must be reported as per local regulatory requirements. The nature and reasons for the protocol deviations will be recorded by the sponsor.

The sponsor may not reimburse the investigator for cases in which the study procedures and evaluations are conducted such that they result in major protocol violations.

11 QUALITY ASSURANCE AND QUALITY CONTROL

11.1 Audit and Inspection

Study centres and study documentation may be subject to quality assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

11.2 Monitoring

Data for each participant will be recorded on a case report form (CRF). Data collection must be completed for each participant who signs a PICF/ICF and is enrolled in the study.

In accordance with the ICH GCP guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable.

The investigator must permit the monitor, the HREC, the sponsor's internal auditors, and representatives from regulatory authorities' direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.

12 ETHICS

12.1 Human Research Ethics Committee/Institutional Review Board Approval

The protocol will be submitted for approval to the appropriate HREC/IRB. Prior to initiation of the study, the investigator must provide the sponsor with a copy of the written HREC/IRB approval of the protocol and study PICF/ICF. This approval letter will identify the study PICF/ICF by date and the study protocol by protocol number, title and date. The investigators will receive all the documentation needed for submitting the present protocol to the HREC/IRB. The composition of the HREC/IRB will also be provided to the sponsor. If approval is suspended or terminated by the HREC/IRB, the investigator will notify the sponsor immediately.

It is the responsibility of the sponsor to report study progress to the HREC/IRB as required or at intervals not greater than 1 year.

The investigator at the study site or his/her nominee, will be responsible for reporting any SAEs to the HREC/IRB as soon as possible, and in accordance with the guidelines of the HREC/IRB.

12.2 Regulatory and Ethical Consideration

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

The investigator will ensure that this study is conducted in full compliance with the protocol, the Declaration of Helsinki, the ICH GCP guidelines, Federal Drug Administration (FDA)/Therapeutic Goods Administration (TGA) regulations, and all other applicable local laws and regulations. Compliance with these standards provides assurance that the rights, safety, and well-being of patients are protected.

In agreeing to the provisions of the protocol, these responsibilities are accepted by the investigator.

12.3 Informed Consent Process

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to ICH GCP guidelines.

The investigator is responsible for ensuring that no participant undergoes any study related examination or activity before that participant has given written informed consent to participate in the study.

The investigator or designated personnel will inform the participant of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The participant should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the participant will be given ample time to consider the study. Participants will be required to sign and date the PICF/ICF. After signatures are obtained, the PICF/ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the PICF/ICF will be provided to the participant or their authorised representative.

It should be emphasised that the participant may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the participant is otherwise entitled. Participants who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, a new PICF/ICF will be approved by the HREC/IRB (and regulatory authorities, if required). Participants will be informed about this new information and reconsent will be obtained.

13 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last participant), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study centre when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study related documentation. In addition, all medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centres in multi centre studies must not be published separately.

14 FINANCING AND INSURANCE

Financing of this study will be outlined in a separate agreement.

Participants may be compensated for the time that they spend participating in the study using a formula determined by the study site.

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

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16 APPENDIX

16.1 WHO Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory Mild Disease	Asymptomatic; viral RNA detected	1
	Symptomatic; Independent	2
	Symptomatic; Assistance needed	3
Hospitalized: Moderate disease	Hospitalized; no oxygen therapy	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: Severe disease	Hospitalized; Oxygen by NIV or High flow	6
	Intubation & mechanical ventilation, pO_2/FIO_2 ≥150 or SpO_2/FIO_2≥200	7
	Mechanical ventilation pO_2/FIO_2<150 (SpO_2/FIO_2 <200) **or** vasopressors	8
	Mechanical ventilation pO_2/FIO_2<150 **and** vasopressors, dialysis, or ECMO	9
Death	Dead	10