Statistical Analysis Plan

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

SAP Version and date: Amendment 1.0, 26-Jul-2021

STUDY DRUG:
INB03

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Contents

ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of variance
ATC	Anatomic Therapeutic Chemical
BMI	Body mass index
CHF	Coronary heart failure
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical trial management system
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
ITT	Intent-to-treat
LCIQ	Long COVID informant questionnaire
LCQ	Long COVID questionnaire
MedDRA	Medical Dictionary for Regulatory Affairs
MI	Myocardial infarction
mITT	Modified Intent-to-treat
MMRM	Mixed model repeated measures
PHQ	Patient health questionnaire
PP	Per protocol
PT	Preferred term
Q1	1st quartile
Q3	3rd quartile
SAE	Serious adverse events
SAF	Safety population
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SofC	Standard of Care
SOC	System organ class
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization
WHODD	WHO Drug Dictionary

1 INTRODUCTION

The statistical analysis plan (SAP) details the planned statistical analysis methods required to address the study objectives as described in protocol INB03-COVID-19_01: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of INB03 in the Treatment of Participants with Pulmonary Complications from Coronavirus Disease (COVID-19).

This SAP should be read in conjunction with the study protocol and case report form (CRF). The version of this SAP is based on the protocol INB03-COVID-19_01, version 12.0 – 17May2021, and CRF version 16.2 – 02Mar2021. Changes to these documents may result in subsequent changes to the SAP. The final, sponsor-approved version of the SAP will be finalized prior to performing the interim analysis of efficacy. SAP updates may be performed subsequent to that analysis. If this occurs, the SAP will be amended and changes to the approved SAP will be listed in Section 1.1 and the amended SAP will be finalized and approved prior to final database lock and unblinding.

1.1 Changes to the Planned Analysis

The protocol mentions a supplemental analysis will be performed on the ITT population. This analysis will not be performed on this population as the objective of the study is to assess the effect study treatment has on disease progression and patients in the ITT population include those that were randomized but not dosed.

The following sensitivity analyses to assess different strategies for handling intercurrent events have been removed from the analysis as the tipping point analysis will be sufficient in determining robustness of imputation methodologies applied.

- 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.

On 15Jun2021, the sponsor terminated enrollment into the study. A preliminary analysis of the primary efficacy data will be performed prior to full database lock. The SAP was written based on the protocol dated 17May2021 therefore some sections of the SAP may no longer be applicable. Changes from the SAP and protocol defined analyses will be described and justified in the final clinical study report.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Efficacy	
Primary	

• 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	• 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	
• To assess the effect INB03 has on all-cause mortality in participants with pulmonary complications from COVID-19 infection	• Proportion of participants with all-cause mortality
• 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	• 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
• To evaluate if treatment with INB03 reduces increase in the WHO Ordinal Scale for Clinical Improvement score	• Proportion of participants with an increase in the WHO Ordinal Scale of Clinical Improvement score at any time during the study
• To evaluate if length of hospital-stay in participants with pulmonary complications from COVID-19 infection decreases when treated with INB03	• 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
• To assess the effect INB03 has on inflammatory markers in participants with pulmonary complications from COVID-19 infection	• Change from baseline in inflammation markers over time
Safety	
• To evaluate the safety and tolerability of INB03 when given to participants with pulmonary complications from COVID-19 infection	• 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	
Efficacy	
• 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	• 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)

3 STUDY DESIGN

3.1 General Description

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 that are performed as part of routine clinical care within 1 day of Screening 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 (SofC) or Placebo SC injection + SofC 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 (including SofC) 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.

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.

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 the Schedule of Assessments (SOA) (Table 3 in the protocol). 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. 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 the SOA (Table 3 in the protocol).

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.

3.2 Randomization and Blinding

Participants who meet inclusion and exclusion criteria and sign informed consent are to be randomized within 1 day of completing screening assessments. Participants will be randomized 1:1 on Study Day 1 in a blinded fashion to either treatment with INB03 at 1 mg/kg + SofC or Placebo + SofC.

Due to the complexity of COVID-19 and the need for immediate randomization, each site pharmacist has been provided with a separate randomization schedule unique to the specific site. The pharmacist at each site is unblinded and is responsible for providing the randomization number to site personnel who further record this information in the electronic case report form (eCRF).

3.3 Sample Size

A total sample size of 366 participants randomized 1:1 to treatment with either INB03 + SofC or Placebo + SofC (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 + SofC will progress whereas the expected disease progression rate will be reduced by two-thirds to 7% in participants randomized to INB03 + SofC. To observe the expected treatment effect, N=346 (N=173 per arm) are required.

Additionally, an interim analysis for futility will be performed once approximately 20% of participants required to observe the expected treatment effect complete the Study Day 28 visit (approximately 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. A customized futility boundary was chosen to ensure a clinically meaningful difference between treatment arms is observed at the interim and which will provide a high conditional power at the time of the final analysis.

The proposed study with the above assumptions will have at least 90% power assuming a one-sided Z-Test with overall alpha for the study of 0.005.

3.4 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will monitor ongoing safety data at pre-specified time points throughout the study. The DMC will also be responsible for reviewing safety/efficacy results at the time of the interim analysis. The main purpose of the DMC will be to protect the interests of the subjects included in the trial.

The DMC charter will define roles and responsibilities of the study team, DMC members and unblinded team, timing of DMC data reviews as well as the type of data required for each data review meeting.

Upon completion of each data review meeting, the DMC will convey to the sponsor their recommendations as to whether the trial may continue as planned or if the trial should be modified or stopped as specified in the DMC charter. The final decision on whether the study should be modified or stopped will be the responsibility of INmune Bio Inc., the 'sponsor'. Any decision to modify or stop the study will be communicated to investigators and regulatory agencies as well as the full study team by the sponsor.

3.5 Timing of Analyses

An interim analysis will be performed once approximately 20% of participants in the mITT population have completed the Study Day 28 assessment or who have an intercurrent event within 28 days on study. Details are included in Section 6.2.4.

The final analysis will occur once all participants complete their end of study visit or their last scheduled assessment per the Schedule of Assessments (Section 8 of the protocol), or the sponsor terminates the study for futility at time of the interim analysis or for any other reason.

4 ANALYSIS POPULATIONS

Intent-to-treat (ITT) Population: 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.

Modified Intent-to-treat (mITT) Population: 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.

Per-protocol (PP) Population: All participants included in the mITT population with no major protocol deviation will comprise the PP population. The PP population will be a secondary analysis population for select efficacy endpoints. Analyses will be based on treatment received. Protocol deviations and assignment to the PP population will be done prior to unblinding.

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

5 GENERAL CONSIDERATIONS

5.1 General Data Handling

All analyses will be conducted using SAS 9.4 or higher. Study data will be recorded in electronic case report forms (eCRFs) designed in the VIEDOC v4.63 electronic data capture (EDC) system. Adverse events will be coded using the version 23.1 of the Medical Dictionary for Regulatory Affairs (MedDRA) and prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODD) September 2020 version.

Protocol deviation data will be provided in spreadsheet format from the clinical trial management system (CTMS). There are no further vendors for this study.

In general, analysis tables will be presented by treatment arm using the following groupings of subjects:

- INB03
- Placebo
- Overall (background characteristics and safety data only)

Data will be presented in by-patient data listings. Unless otherwise stated, all listings will be sorted by treatment arm, center ID, subject number, and assessment date (and time, if available).

Continuous data will be summarized by treatment group based on number of participants (n), mean, standard deviation (SD), median, minimum value, and maximum value. In some cases, first quartile (Q1) and third quartile (Q3) may also be included.

Categorical data will be summarized by treatment arm using frequency counts and percentages. Where applicable, 95% confidence intervals (CIs) will be provided. Unless otherwise stated, the denominator of percentages will be the number of participants in the population/treatment arm or the number with non-missing data.

- The number of missing values will be presented as a separate category with no percentage, but only if one or more subjects are missing data.
- Counts of zero will be presented without percentages.

Relative to the number of digits after the decimal in the raw data, summary statistics will have the following number of digits after the decimal:

- Minimum and Maximum: same number of significant digits as the raw data
- Mean, Median, Q1, and Q3: one additional significant digit
- SD or Standard Error (SE): two additional significant digits
- Percentages <100% will be reported to one decimal place and percentages of 100% will be reported with no decimal place.
- P-values will be reported to four decimal places. If the value is below 0.0001 it will be noted as < 0.0001; if the value is above 0.9999 it will be noted as > 0.9999.
- Summary statistics will not exceed four digits after the decimal. Some laboratory parameters or other data may require judicious deviation from this rule.

Unless otherwise noted, statistical inference will be based on a 2-sided 1% significance level.

All data up to the time of study completion/withdrawal from the study will be included in the analysis, regardless of duration of treatment.

Numbering for data displays will be based on ICH E3.

5.2 General Definitions

Variable	Definition
Study Day	• Study Day = date of interest – reference date + 1, when the date of interest >= reference date; • otherwise, Study Day = date of interest – reference date. Note: if either day is missing, reference date calculations will not be performed. Should imputation be performed, then Study day may be derived.
Baseline	Defined as the last non-missing value collected prior to receiving the first dose of study treatment (based on date and time of administration as applicated).
Post-baseline	Defined as values collected after receipt of the first dose of study treatment (based on date and time of administration as applicable)
Change from Baseline	Defined as: Post-baseline value – Baseline value

Percent Change from Baseline	Defined as: (Post-baseline value – Baseline value)/Baseline value x 100. Note: To compute percent change from baseline, the baseline value cannot be equal to zero.
Duration on Study	End of study date – randomization date +1.
Disease Onset	Self-reported start date of first COVID-19 symptom – date of first dose of study treatment. Time will be considered in the derivation if collected for both dates. If the self-reported date is missing, the date of positive COVID-19 test will be used.
Duration of Adverse Event (in days)	• Stop date of event – start date of event + 1, if time is not collected. • (Stop date/time of event – start date/time of event)/24, if time is collected.
Months	Divide by 30.4375
Year	Divide by 365.25
Week	Divide by 7

5.3 Data Imputation Rules

Generally, missing data will not be imputed, and will be presented as collected in the study database.

In cases where AE or medication dates are missing, the imputation methods described in Appendix 1 will be used to determine flags for treatment-emergent events and concomitant medications.

For interim reporting purposes or ongoing reporting needs, treatment or study end dates will be imputed as the earliest of the data cutoff date, date of death, or date of treatment study withdrawal.

Other missing data methods specific to statistical analysis will be proposed within the respective analysis section, as needed.

5.4 Visit Windows

In general, data will be summarized and listed using the recorded nominal visit values in the eCRF, regardless of the actual study day on which a value was collected. Unscheduled visits will not be summarized in tables but will be presented in data listings.

5.5 Pooling of Sites

Sites will be pooled for all analyses.

6 ANALYSIS METHODS

6.1 Study Patient Data

6.1.1 Patient Enrollment and Disposition

The number and percentage of patients in each analysis population and final patient status (completed or withdrawn), including reasons for withdrawal, will be produced based on the number of randomized patients. In addition, the number of patients receiving 1 or 2 doses of study treatment will be presented. Data will be presented by treatment arm and overall. Patients who were enrolled and not randomized will be included in the overall column.

Patients contributing to each analysis populations and final patient disposition status will be listed.

6.1.2 Protocol Deviations

Protocol deviations will be identified and classified as minor or major (violations) before the database is locked. Major protocol deviations include and are not limited to:

- Violation of Inclusion/Exclusion Criteria
- Signed incorrect version of patient consent form
- Use of prohibited therapies
- Receiving incorrect randomized treatment
- Did not receive mechanical ventilation due to the machine not being available

Each protocol deviation will be reviewed prior to database lock and the deviations that are identified as having an impact on the primary study endpoint will be flagged and patients with those deviations will be excluded from the PP population.

Protocol deviations will be summarized by treatment arm and overall for the study.

A listing of protocol deviations will be provided.

6.1.3 Demographic and Baseline Characteristics

Patient demographics will be summarized and listed for patients in the ITT population. Reports will include age as a continuous variable as a categorical variable (≤50, >50 to 65, >65), gender, ethnicity, race, smoking status, baseline height (cm), baseline weight (kg), and BMI (kg/m^2). Data will be presented by treatment arm as well as overall for the study.

COVID-19 disease history will be summarized and listed. These will include: number of comorbidities, the number and percentage of patients with 1, 2, or 3+ comorbidities, number of symptoms at time of hospitalization and a breakdown by symptom (n and %), days since self-reported first symptom, days since self-reported fever, days since date of positive test. Derivation of ‘days since’ variables will use date of randomization as the reference date.

6.1.4 Medical History

Medical history will be collected during screening and will be summarized by MedDRA coded system organ class (SOC) and preferred term (PT) by treatment arm and overall. All patient data will also be listed.

The following co-morbidities will be identified based on medical history and will be summarized in addition to the overall medical history. Medical co-morbidities include:

- Hypertension
- Diabetes
- Cardiovascular disease
- Congestive heart failure or myocardial infarction

6.1.5 Prior and Concomitant Medication

Prior medication collection was limited to medications required for review of entry criteria. Current medications and new medications prescribed while on study were collected in the eCRF. Medications will be summarized by anatomical therapeutic chemical (ATC) level 2 classification and preferred name as coded by WHODD. A subject will be counted only once at each level of reporting.

Prior medications are those which have been identified to have been discontinued prior to the treatment start date. Concomitant medications are those with a start date prior to date of first dose of study treatment and ongoing at time o

f treatment or which have been prescribed and taken after first dose of study treatment. Prior medications will be listed only. Concomitant medication will be summarized and presented by treatment group.

All prior and concomitant medication data will be listed including the verbatim and preferred drug name and ATC Level 2.

6.1.6 Study Drug Exposure and Compliance

Patients randomized to study treatment are to receive their first dose on Day 1 and a second dose on Day 8. All effort will be made for patients who remain in the hospital on Day 8 to receive their second dose of study treatment. If the patient is discharged prior to Day 8, no second dose will be administered.

Compliance will not be assessed in this study as sites are administering study treatment. As the disease in nature may progress quickly, the expectation is that at least 1 dose of study treatment will be given.

The number and percentage of patients who receive 1 dose and 2 doses will be summarized by treatment arm and overall. The planned dose level and total dose administered will be descriptively summarized by dose received.

Study treatment administration details, including reasons for not administering drug and if there were issues with the administration will be listed.

6.2 Efficacy

Analyses and summary statistics will be reported on the mITT population. Efficacy endpoints are assessed up to Day 28. All data will be listed. Sensitivity and supplemental analyses may be repeated in other analysis populations.

6.2.1 Primary Efficacy Endpoint and Analyses

The primary objective of the study is to evaluate the effect INB03 + SofC has on disease progression compared with placebo + SofC. Disease progression is defined as death or requirement for mechanical ventilation in participants with pulmonary complications from COVID-19 infection. The primary endpoint to assess the objective is to compare the proportion of patients who reach disease progression in both treatment arms. Disease progression will be assessed up to Day 28. Patients will be identified as follows:

1 = Disease progression – defined as developing the need for mechanical ventilation or death by Day 28. Mechanical ventilation includes CPAP, BIPAP, or mechanical ventilation requiring intubation.

0 = No disease progression – defined as not developing the need for mechanical ventilation or death by Day 28

The null hypothesis is that there is no difference in the proportion of patients who have disease progression between treatment groups and the alternative is that the proportion of INB03 treated patients with disease progression is less than the proportion of placebo patients with disease progression.

$$H_0: P_{INB03} = P_{Placebo} \text{ vs } H_1: P_{INB03} < P_{Placebo}$$

Statistical analysis of the primary endpoint will be performed with a one-sided level of significance and final alpha of α=0.005.

6.2.1.1 Primary Estimand

Treatment Arms	INB03 (1mg/kg) + SofC and Placebo + SofC, given via subcutaneous injection.
Target Population	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.
Endpoint	Proportion of participants with disease progression from randomization to 28 days post-randomization. Disease progression is defined by the development of need for mechanical ventilation or death. Mechanical ventilation includes CPAP, BIPAP or mechanical ventilation requiring intubation.

Population Summary	Difference between treatment arms in proportion of disease progression by day 28	
Analysis Method	Stratified Cochran-Mantel-Haenszel	
Intercurrent events	**Event**	**Strategy**
	Withdraw consent prior to Day 28	While on treatment – data prior to event is of interest
	Lost to Follow-up prior to Day 28 with no hospital discharge date	Composite variable – event is considered informative about patient's outcome
	Lost to Follow-up prior to Day 28 with a hospital discharge date	Treatment policy – data is used as if event never occurred
	Did not receive Dose 2 on Day 8	Treatment policy – data is used as if event never occurred
	Discontinued from study for reasons other than Withdrawal of consent or Lost to Follow-up prior to Day 28	Treatment policy – data is used as if event never occurred
	Receipt of prohibited medication prior to Day 28	Treatment policy – data is used as if event never occurred
	Did not receive mechanical ventilation due to unavailability	Hypothetical – data is used assuming event did not occur

6.2.1.2 Primary Analysis

The primary endpoint is binary in nature and will be analyzed using 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, 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 will be combined for the analysis as follows:

- Age will be split by the median in the mITT population (ie: < median, >= median)
- 1-2 comorbidities vs. 3+ comorbidities

If still not sufficient, a non-stratified Chi-square analysis will be conducted instead of CMH.

The number and percentage of patients with disease progression by Day 28 will be summarized by treatment arm.

6.2.1.3 Handling Missing Data

The following intercurrent events may lead to missing data for the primary endpoint. Imputation will be performed when the primary endpoint of mechanical ventilation or death information prior to Day 28 is missing.

Intercurrent Event	**Strategy**	**Method of handling missing data**
Withdraw consent prior to Day 28	While on treatment – data prior to event is of interest	the last available post-randomization record of the WHO Ordinal Scale for Clinical Improvement, prior to the intercurrent event, will be used to assess disease progression
Lost to Follow-up prior to Day 28 with no hospital discharge date	Composite variable – event is considered informative about patient's outcome	the participant will be considered to have disease progression
Lost to Follow-up prior to Day 28 with a hospital discharge date	Treatment policy – data is used as if event never occurred	the last available post-randomization record of the WHO Ordinal Scale for Clinical Improvement, prior to the intercurrent event, will be used to assess disease progression
Discontinued from study for reasons other than Withdrawal of consent or Lost to Follow-up prior to Day 28	Treatment policy – data is used as if event never occurred	the last available post-randomization record of the WHO Ordinal Scale for Clinical Improvement, prior to the intercurrent event, will be used to assess disease progression
Did not receive mechanical ventilation due to unavailability	Hypothetical – data is used assuming event did not occur	the last available post-randomization record of the WHO Ordinal Scale for Clinical Improvement, prior to the intercurrent event, will be used to assess disease progression

6.2.1.4 Sensitivity Analyses

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. The analysis population will be the mITT population.

6.2.1.5 Supportive and Supplemental Analyses

The primary analysis will be repeated using the PP population. The strategies considered for handling intercurrent events will be the same in this analysis as for the primary analysis in the mITT population.

A supportive analysis will be performed on the primary endpoint 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, odds ratio and the corresponding 95% CIs will be provided. The strategies for handling intercurrent events will be the same in this analysis as for the primary analysis, and the population for analysis will be the mITT population.

6.2.2 Secondary Efficacy Endpoints and Analyses

Secondary efficacy endpoints will be analyzed for patients included in the mITT population. No adjustment for multiplicity is planned therefore nominal p-values will be provided for secondary endpoints. All data on the secondary endpoints will be provided in data listings.

6.2.2.1 Continuous Endpoints

Descriptive statistics will be provided for each endpoint and will be reported by treatment arm. Endpoints that are not normally distributed will also display geometric means. Absolute values and changes from baseline will be presented for the following:

- Inflammation markers (COVID-19 Specific markers: eGRF, Troponin, CRP, Ferritin, D-dimer)
- WHO Ordinal Scale for Clinical Improvement

Baseline will be defined as the value in the database prior to receiving any amount of study treatment. Line plots of means with error bars for the above endpoints will be presented by treatment group. Figures of means for both absolute values at each timepoint and the changes from baseline will be provided.

Changes from baseline will further be analyzed statistically using a mixed model repeated measures (MMRM) analysis. Factors include treatment arm, timepoint, age (≤50, >50 to 65, >65) and number of co-morbidities (1, 2, 3+). The baseline value of the endpoint will be included as the covariate. Patient will be repeated by timepoint. An unstructured covariance and the Kenward Roger's approximation for the degrees of freedom will be assumed. Least-square means will be provided for the treatment differences (INB03 + SofC vs Placebo + SofC) as well as the corresponding 95% CIs.

Descriptive statistics will be provided for the following endpoints and reported by treatment arm.

- Length of stay in index hospital
- Days to disease progression

Length of stay in index hospital will be derived as the index hospital discharge date – randomization date +1. Time will be considered in the derivation if collected for both dates. If discharge date is missing, date of death or end of study date will be used, whichever comes first.

Days to disease progression is not a specified secondary endpoint in the clinical study protocol, however is of interest to summarize. Days to disease progression will be derived as the first date of disease progression – randomization date +1. Intercurrent events, as defined in Section 6.2.1.3, will be considered when assigning a patient as having disease progression. Patients with no disease progression and who have completed the study will be censored as the duration on study. Patients who terminated the study early and with no disease progression according to Section 6.2.1.3 will be censored and given the longest duration, 40 days.

A multi-factor analysis of variance (ANOVA) will be used to assess the differences between treatment arms for each endpoint. Treatment arm, age (≤50, >50 to 65, >65) and number of co-morbidities (1, 2, 3+) will be included as factors in the model. Least-square means will be provided for the treatment differences (INB03 + SofC vs Placebo + SofC) as well as the corresponding 95% CIs. If assumptions for ANOVA are not met then a comparable non-parametric test will be performed (e.g., rank ANOVA or Wilcoxon rank-sum tests).

6.2.2.2 Binary Endpoints

Binary secondary endpoint will be summarized with number and percentage of patients with the criteria. The denominator for percentages will be the patients included in the treatment arm for the mITT population who have data for the endpoint. The following endpoints assessed up to Day 28 visit will be summarized by treatment arm:

- Proportion with 1 point, 2 point etc. increase/decrease in WHO Ordinal Scale
- Proportion with all-cause mortality at any time
- Proportion who transfer to ICU level care
- Proportion with a new onset of neurological disease
- Proportion with evidence of new CHF or new MI requiring medical intervention
- Proportion with new onset of embolus or thrombus
- Proportion who develop need for renal replacement therapy

Data on endpoints are directly captured in the eCRF. In the case of intercurrent events, the treatment policy strategy will be considered and the last-available record in the EDC prior to or on Day 28 will be used for reporting these events.

The statistical analyses for secondary endpoints with binary outcomes will be performed using CMH tests similar to the primary estimator.

6.2.3 Exploratory Efficacy Endpoints and Analyses

Exploratory efficacy endpoints will be summarized for patients included in the mITT population. No analyses will be performed. All data will be provided in data listings.

The presence and frequency of depressive symptoms are assessed through the Patient Health Questionnaire-9 item version (PHQ9). There are 9 questions with scores ranges from 0=”not at

all" to 3="nearly every day". The total score is 27. Summary statistics will be presented by treatment arm for the Day 40 results.

Two Long COVID questionnaires are to be completed on Day 40, or by ePRO/telephone between Day 40 and 50. One by the patient and the other by an informant.

The Long COVID Questionnaire (LCQ) is self-administered to assess symptoms of Long COVID. The LCQ contains a series of questions asking the patient to compare current health and abilities to pre-COVID health and abilities with subscales that collect information on 1) Functioning and Performance, 2) Somatic symptoms, and 3) Cognitive complaints. The questionnaire further collects changes in life circumstances extrinsic to COVID-19 disease. The total score and scores for each subscale will be summarized descriptively by treatment arm.

Patients with clinically meaningful changes in pre-COVID health and abilities (changes in subscale 1, 2, or 3) on Day 40 will be considered as having Long COVID symptoms and will be summarized (N and %) by treatment arm.

A second Long COVID questionnaire will be completed by an informant (Long COVID Informant Questionnaire (LCIQ)). Seventeen items will be completed by the informant to understand the informant's perspective on changes in life functioning temporally associated with COVID-19 disease onset. Responses to the items (total score and subscale scores) will be descriptively summarized by treatment arm.

6.2.4 Interim Analysis

An interim analysis will be performed once approximately 70 patients (20% of information) in the mITT population have completed the Study Day 28 assessment or who have an intercurrent event within 28 days on study leading to missing primary efficacy data. All patients up to the data cutoff date for the interim analysis will be included in the analysis. Imputation of missing data will be performed as described in Section 6.2.1.3.

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-scores. The Z-score 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, there must be at least a 7.5% treatment difference observed. Assuming the 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 -0.8805 (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. Details included in the DMC charter.

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.

On 15Jun2021, the sponsor terminated enrollment into the study. Participants who were enrolled and randomized on or before 15 June were followed to study completion and will be included in the primary efficacy analysis. A total of 79 subjects were randomized, 77 receiving randomized study drug.

A preliminary analysis of the primary efficacy data will be performed prior to the final database lock. The primary efficacy endpoint will be analysed 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 unblinded team will provide the DMC and select individuals from INmune Bio. the unblinded primary efficacy results. Only the DMC will receive unblinded safety data. The DMC and unblinded sponsor team will collaborate directly with the unblinded statistical team for further support as needed. The statistical study team will not be in contact with the unblinded sponsor team.

A final analysis will occur once all subjects complete the study.

6.2.5 Multiplicity

Formal statistical analysis will be performed for the primary efficacy endpoint. All p-values displayed for the secondary efficacy endpoints will be nominal in nature. No multiplicity adjustments will be performed for multiple analyses or multiple endpoints.

6.2.6 Subgroup Analyses

Subgroup analyses may be performed outside the scope of the SAP.

6.3 Safety

Safety assessments will include current standard of care in the hospital setting. Assessments such as vital signs will be assessed daily while the patient is in the hospital. COVID-19 labs will also be assessed every other day and additionally as requested by the physician. Safety assessments including but not limited to chest imaging, ECG, safety labs (hematology, chemistry) will be performed at the discretion of the physician.

All safety analysis reporting will be based on the Safety Population.

6.3.1 Adverse Events

Adverse events (AEs) will be recorded from study enrolment until study Day 70. AEs will be assessed for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, relationship to study drug, and seriousness. Adverse events will be considered treatment-emergent if the event was a pre-existing condition that increases in severity, becomes serious after start of study treatment, or if the onset of the event occurs after the first dose of study treatment. Any missing severity assessments will be assumed as Grade 3 severity and missing relationship assessments will be assumed as related.

An overview of treatment-emergent AEs (TEAEs) will be provided, including counts and percentages of patients with any incidences of: TEAEs, TEAEs related to study treatment, serious adverse events (SAEs), TEAEs leading to study discontinuation, SAEs, and fatal SAEs.

Adverse events will also be displayed by MedDRA coded system organ class (SOC) and preferred term (PT) in descending order of overall incidence. Data will be reported by treatment arm and overall.

Summaries of adverse events by SOC and PT will be provided for the following:

- TEAEs;
- TEAEs related to study treatment;
- CTCAE Grade 3 or higher TEAEs;
- CTCAE Grade 3 or higher TEAEs related to study treatment;
- SAEs; and
- TEAEs leading to study discontinuation.

When calculating the incidence of AEs, each AE will be counted only once for a given patient within a MedDRA category (e.g. overall, system organ class or preferred term). When AEs are summarized within levels of another AE assessment (e.g., relatedness or severity), AEs will be counted once per patient at the worst level of the assessment (e.g., strongest relationship to study drug or greatest severity).

A comprehensive listing of all AEs reported will be provided in a by-patient data listing. In addition, the following listings will be provided:

- TEAEs related to study treatment;
- SAEs;
- TEAEs leading to study discontinuation; and
- Fatal AEs.

6.3.2 Clinical Laboratory Evaluations

Safety laboratory data will be collected at the site and reported locally. Haematology and clinical chemistry are optional in reporting during the hospital setting and will be collected as per standard of care for the patient while in the index hospital. Safety laboratory collection is required at screening, upon discharge and on Day 28 and Day 40.

As collection date may vary, by-patient listings will be provided and abnormal results will be flagged. Change from baseline will be provided in the listing. A separate listing for abnormal and clinically significant lab results will be provided if there is data to support this listing.

Clinical chemistry and haematology parameters will be reported based on the International System of Units (SI).

Pregnancy test is only performed at screening in women of childbearing potential, test results will be listed.

6.3.3 Vital Signs

Vital sign assessments will be performed each day the patient is in the index hospital. Observed values and changes from baseline in each vital sign parameter will be summarized by study day and reported by treatment arm. Vital sign parameters include: weight (kg, screening only), height (cm, screening only), BMI (kg/m^2, screening only), systolic and diastolic blood pressure (mmHg), respiratory rate (breaths/m), heart rate (beats/min) and body temperature (F).

6.3.4 Electrocardiogram

Electrocardiogram (ECG) may be performed throughout the time the patient is in the index hospital as part of routine care. ECGs will be performed at screening, on Day 28 and Day 40. If these visits are conducted remotely, the ECG may be omitted.

Data collected in the eCRF includes the overall evaluation of the ECG, either normal, abnormal and not clinically significant or abnormal and clinically significant. Listings of data collected with be provided by patient.

6.3.5 Physical Examinations

Physical examinations will be collected as per standard of care and details are not collected on the CRF. Any abnormal and clinically significant findings will be captured as AEs and reported as suck..

6.3.6 Other

6.3.6.1 Non-mechanical ventilation

Use of non-mechanical ventilation is assessed each day the patient is in the index hospital. The number and percentage of patients with non-mechanical ventilation use, the delivery system used and the total number of days with non-mechanical ventilation use will be summarized by treatment arm. All data will be provided in by-patient listings.

6.3.6.2 Chest Imaging

Lung imaging (X-ray, MRI, or CT) will be performed at screening to confirm pulmonary disease due to COVID-19. Imaging may also be performed throughout the time the patient is in the index hospital as deemed clinically relevant for standard of care. Images post-study treatment will be evaluated for any changes (same, worsening, improvement) compared with a previous image and data will be provided in a by-patient listing. Images that worsen compared with a previous image will be flagged in the listing.

6.3.6.3 SaO2

Room air SaO2 will be collected at screening, at hospital discharge, Day 28 and Day 40. Observed values and changes at each timepoint of collection will be reported. Collection of SpO2 on room air at sea level and PaO2/FiO2 will be listed. All data will be included in patient listings.

6.3.6.4 Anti-drug Antibody

The development of anti-drug antibodies will be assessed. Blood samples will be collected prior to dosing with study treatment and at the Day 28 and Day 40 visits and will be analyzed at a central laboratory. A listing of anti-drug antibody data will be provided.

6.3.6.5 TNF Blood Levels

Blood samples to assess TNF levels will be collected on Day 1 prior to dosing with study treatment. Results will be included in patient a listing.

7 APPENDICES

7.1 APPENDIX 1: Partial Date Conventions

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study drug start date, then not TEAE If start date >= study drug start date, then TEAE *if time is collected, consider time in determining if event is a TEAE
Partial, but known components show that it cannot be on or after study drug start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE *if time is collected, consider time in determining if event is a TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing or ongoing is checked	TEAE
Missing	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE *if time is collected, consider time in determining if event is a TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing or ongoing is checked	TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known/Partial/Missing	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Missing	If stop date is missing, assign as concomitant If "Ongoing" is flagged, assign as concomitant

7.2 APPENDIX 2: Estimand Terminology

Source: ICH E9 R1

Strategy	**Description**
Treatment policy	The occurrence of the intercurrent event is irrelevant: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.
Composite Variable	The occurrence of the intercurrent event is taken to be a component of the variable, i.e. the intercurrent event is integrated with one or more other measures of clinical outcome as the variable of interest.
Hypothetical	A scenario is envisaged in which the intercurrent event would not occur: the value to reflect that scientific question of interest is that which the variable would have taken in the hypothetical scenario defined.
Principal stratum	The target population might be taken to be the principal stratum (see Glossary) in which an intercurrent event would not occur.
While on treatment	Response to treatment prior to the occurrence of the intercurrent event is of interest.