# STATISTICAL ANALYSIS PLAN (RotW)

## Protocol: SG018

Version 5.0 09SEP2021

A randomised, double-blind, placebo-controlled, Phase III trial to determine the efficacy and safety of inhaled SNG001 for the treatment of patients hospitalised due to moderate COVID-19

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## 2 Abbreviations and Definitions

| | |
|---|---|
| ADaM | Analysis Data Model |
| AE | Adverse Event |
| ATC | Anatomical Therapeutic Chemical |
| CCI | CCI |
| BCSS | Breathlessness, Cough and Sputum Score |
| BMI | Body Mass Index |
| CDISC | Clinical Data Interchange Standards Consortium |
| CI | Confidence Interval |
| CIF | Cumulative Incidence Function |
| CCI | CCI |
| COPD | Chronic Obstructive Pulmonary Disease |
| COVID-19 | Coronavirus Disease 2019 |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| DSMC | Data Safety Monitoring Committee |
| ECG | Electrocardiogram |
| EQ-5D-5L | EuroQol-5 Dimensions-5 Levels Quality of Life Questionnaire |
| FACIT | Functional Assessment of Chronic Illness Therapy |
| GAD-7 | General Anxiety Disorder-7 Questionnaire |
| ICH | International Council for Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IMP | Investigational Medical Product |
| ITT | Intent-to-Treat |
| LS | Least Square |
| LSS | Level Sum Score |
| MAR | Missing at Random |
| MCMC | Monte Carlo Markov Chain |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MIU | Million International Units |
| MMRM | Mixed Model for Repeated Measures |
| NEWS2 | National Early Warning Score 2 |
| OSCI | Ordinal Scale for Clinical Improvement |
| PHQ-9 | Patient Health Questionnaire-9 |
| PP | Per Protocol |
| PT | Preferred Term |
| PK | Pharmacokinetics |
| RMST | Restricted Mean Survival Time |
| RT-PCR | Reverse Transcription Polymerase Chain Reaction |
| SAE | Serious Adverse Events |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| SDTM | Study Data Tabulation Model |
| SMF | Study Master File |
| SNG001 | The investigational drug product - an inhaled IFN-β1a formulation for nebulisation |

| | |
|---|---|
| SOC | System Organ Class |
| TEAE | Treatment Emergent Adverse Event |
| TFLs | Tables, Figures and Listings |
| CCI | CCI |
| TMF | Trial Master File |
| VAS | Visual Analogue Scale |
| WHODD | World Health Organisation Drug Dictionary |

# 3 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide all information that is necessary to perform the required statistical analyses of study SG018 for submission to all regulatory authorities outside of the the United States of America. It also defines the summary Tables, Figures and Listings (TFLs) to be included in the final clinical study report according to the protocol. The SAP is based upon, and assumes familiarity, with the study protocol, version 5.0, dated 9th September 2021.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. The content of this SAP is compatible with the International Council of Harmonisation (ICH) E9 Guidance document.

# 4 Study Objectives and Endpoints

## 4.1 Study Objectives

### 4.1.1 Primary Objective

To evaluate recovery in patients with moderate Coronavirus Disease 2019 (COVID-19) after administration of SNG001 compared to placebo.

### 4.1.2 Secondary Objective

- To evaluate the efficacy of SNG001 compared to placebo in patients with moderate COVID-19, using a range of endpoints.
- To assess the general safety and tolerability of SNG001 compared to placebo when administered to patients with moderate COVID-19.

### 4.1.3 Exploratory Objective

CCI [redacted]

## 4.2 Endpoints

### 4.2.1 Primary Endpoints

- Time to hospital discharge, defined by the WHO OSCI score of 2 or below, with no rebound at subsequent assessments.
- Time to recovery, where recovery is defined as the World Health Organisation (WHO) OSCI score of 1 or below, with no rebound at subsequent assessments.

### 4.2.2 Key Secondary Endpoints

- Progression to severe disease or death, defined by the WHO OSCI score of 5 or above within 35 days of first dose.
- Progression to intubation or death, defined by the WHO OSCI score of 6 or above within 35 days of first dose.
- Death within 35 days of first dose.

### 4.2.3 Secondary Endpoints

- Recovery, where recovery is defined as the WHO OSCI score of 1 or below, with no rebound at subsequent assessments, at Days 7, 14, 21 and 28.
- Hospital discharge at Days 7, 14, 21 and 28.
- Improvement across the entire WHO OSCI at Days 7, 14, 21 and 28.
- Changes in Breathlessness, Cough and Sputum Scale (BCSS) score during the study period, including disaggregated breathlessness and cough scores.
- Changes in National Early Warning Score (NEWS)2 during the hospitalisation period.
- Daily assessment of COVID-19 symptoms and limitation of usual activities.
- Quality of life measured using EuroQol 5-dimension 5-level (EQ-5D-5L).
- Long-COVID-19 symptoms.
- Safety and tolerability – vital signs, adverse events (AEs) and concomitant medications.

### 4.2.4 Exploratory Endpoint

CCI [redacted] CCI [redacted]

## 5 Study Methods

### 5.1 General Study Design and Plan

610 adults, ≥18 years of age with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection confirmed by a positive virus test using a validated molecular assay e.g. Reverse Transcription Polymerase Chain Reaction (RT-PCR) or antigen assay, e.g. Sofia 2 SARS Antigen FIA, who are hospitalised due to COVID-19 and require oxygen therapy, either via nasal prongs or a mask, but do not require high-flow nasal oxygen therapy, non-invasive ventilation (Continuous Positive Airway Pressure [CPAP] or /bilevel positive airway pressure [BiPAP]) treatment or endotracheal intubation will be randomised 1:1 to receive SNG001 two syringes (305 patients) or placebo two syringes (305 patients).

Patients will receive a dose of SNG001 or placebo once a day for 14 days and will be followed for up to 90 days after the first dose of study medication. Study data will be collected from patients daily until day 35, as per the study schedule.

### 5.2 Randomisation and Blinding

This is a double-blind study. Patients will be randomised to one of two treatment groups (SNG001 or placebo) in a 1:1 randomisation ratio. Randomisation is stratified by study site.

- Arm 1: 305 patients - SNG001 - contents of 2 syringes* per dose.
- Arm 2: 305 patients - Placebo - contents of 2 syringes+ per dose.

* Each syringe contains CCI mL of SNG001 nebuliser solution containing CC MIU/mL interferon-β1a.
+ Each syringe contains CCI mL of formulation buffer.

Data provided for Data Safety Monitoring Committee (DSMC) meetings will be unblinded, starting from the second DSMC meeting as per DSMC charter version 2. An independent statistical team will be responsible for generating the unblinded outputs provided to the DSMC and will not be involved in any future decisions regarding study conduct.

Unblinded data will also be provided for the futility analysis and will therefore be provided by an independent statistical team who will not be involved in any future decisions regarding study conduct. Futility analysis outputs will be reviewed by the DSMC acting as the Independent Data Monitoring Committee (IDMC), as documented in the DSMC charter.

The main study team will remain blinded until the primary analysis, which will be conducted once all patients have withdrawn, or completed the day 35 assessment.

For further information regarding study unblinding, refer to the study unblinding plan.

## 5.3 Derived variables

Unless otherwise specified, baseline is defined as the last non-missing pre-treatment assessment prior to first dose. For patients who are randomised but do not receive any study treatment baseline will be defined as the pre-treatment assessment.

### 5.3.1 Derivations from the Ordinal Scale for Clinical Improvement

#### *5.3.1.1 Hospital Discharge*

Hospital discharge will be defined as the first post baseline score of ≤2 which is sustained for a minimum of 7 days and up to the date of the Day 35 assessment or study withdrawal, whichever occurs first (see Section 15 for changes from the protocol) according to the WHO 9-point Ordinal Scale for Clinical Improvement (OSCI)[1]. If any OSCI assessments are missing following discharge, sustained hospital discharge will be confirmed by the subject's location on the assessment day, which will be recorded in the CRF as "In Hospital" or "Not in Hospital" and may be entered retrospectively. If location is missing, the patient will be assumed to be not in hospital under the assumption that any hospitalisations prior to the last completed assessment will be recorded in the clinical database. This will not include assessments missing following study withdrawal if study withdrawal occurs within 7 days of hospital discharge. If a patient withdraws from the study within 7 days of hospital discharge, they will not be considered as discharged. Hospital discharge will be derived for all scheduled post-baseline assessments up to day 28.

Time to hospital discharge (in days) for discharged patient will be calculated as the following:

Date of first hospital discharge – date of randomisation + 1

Because OSCI score is collected up to day 35, the latest possible hospital discharge date will be at the Day 28 assessment (because it must be sustained for a minimum of 7 days). Patients who die will be administratively censored at the maximum time to hospital discharge. Patients who are not discharged for a minimum of 7 days will be considered censored at the date of their last OSCI assessment of 3 or above. Time to censoring will be calculated as the following:

Date of last OSCI assessment >2 on or before Day 28 – date of randomisation + 1.

#### *5.3.1.2 Recovery*

Recovery will be defined as the first post baseline OSCI score of ≤1 which is sustained for 7 days (see Section 15 for changes from the protocol). A maximum of 3 missing OSCI assessments will be permitted during the rebound period, provided all observed OSCI assessments in the rebound period are 1 or below. If more than 3 assessments are missing the patient will not be considered as recovered at that date and sustained recovery will be reassessed at the subsequent OSCI assessment ≤1, if applicable, or otherwise censored according the rules below. This will not include assessments missing due to study withdrawal. If a patient withdraws from the study during the 7 day rebound period they will be considered not recovered. Recovery will be derived for all scheduled post-baseline assessments up to Day 28.

Time to recovery (in days) for recovered patients will be calculated as the following:

Date of first OSCI score of ≤1 – date of randomisation + 1.

Because OSCI score is collected up to day 35 the latest date of recovery will be at the Day 28 assessment. Patients who die will be administratively censored at the maximum time to recovery. Patients who potentially recover, but cannot be confirmed due to missing data (i.e. after an OSCI ≤1 all observed assessments in the subsequent 7 days were ≤1 but more than 3 assessments were missing) will be censored at the assessment immediately prior to the potential date of recovery. All other patients who do not recover for a minimum of 7 days will be considered censored at the date of their last OSCI assessment of 2 or above on or before day 28. Time to censoring will be calculated as the following:

Date of last OSCI assessment >1 on or before day 28 – date of randomisation + 1

#### *5.3.1.3 Progression to Severe Disease or Death within 35 days of First Dose or Randomisation*

Severe disease is defined by the OSCI as a score between 5 and 7. Death is defined by an OSCI score of 8. Any patient with an OSCI score at any post baseline assessment up to and including Day 35 of 5 or more will be considered as progressed to severe disease or death.

All patients should have an OSCI score of 4 at baseline, however in the event a patient is randomised with an OSCI score of ≥5 at baseline this patient will be excluded from all analyses of progression to severe disease or death.

Day 35 will be determined by the study schedule, which may be more than 35 days after randomisation if randomisation occurs before Day 1.

#### *5.3.1.4 Progression to Intubation or Death within 35 days of First Dose or Randomisation*

Intubation is defined by the OSCI as a score between 6 and 7. Death is defined by an OSCI score of 8. Any patient with an OSCI score at any post baseline assessment up to and including Day 35 of 6 or more will be considered as progressed to intubation or death.

All patients should have an OSCI score of 4 at baseline, however in the event a patient is enrolled with an OSCI score of ≥6 at baseline this patient will be excluded from all analyses of progression to intubation or death.

Day 35 will be determined by the study schedule, which may be more than 35 days after randomisation if randomisation occurs before Day 1.

#### *5.3.1.5 Death within 35 days of First Dose or Randomisation*

Deaths will be identified by an OSCI score of 8 at any post baseline assessment up to and including Day 35, a fatal Adverse Event (AE) on or before Day 35 or withdrawal due to a fatal AE on or before Day 35. Patients who die after Day 35 will be considered alive for the derivation of death within 35 days of first dose or randomisation.

Day 35 will be determined by the study schedule, which may be more than 35 days after randomisation if randomisation occurs before Day 1.

### 5.3.2 Derivation of NEWS2 Scores

The NEWS2 score will be calculated using the following six parameters:

1. respiration rate
2. oxygen saturation
3. systolic blood pressure
4. pulse rate
5. level of consciousness or new confusion
6. temperature.

Each parameter will be assigned a score between 0 and 3 according to the chart in Appendix I and the NEWS2 score is calculated as the sum of the individual parameter scores, providing that all respective scores are non-missing. If any individual parameter scores are missing the NEWS2 score will also be missing.

For the pre-treatment/pre-baseline assessment, the NEWS2 score will be derived using data from scheduled vital signs page of the eCRF. For any post-baseline assessments, the NEWS2 score will be derived using data from the scheduled NEWS2 page.

NEWS2 score will also be categorised as per table 1.

**Table 1: NEWS2 Clinical Risk Categories**

| Criteria | Clinical Risk Category |
|---|---|
| NEWS2 score between 0 and 4 | Low |
| Score of any individual parameter of 3 | Low-medium |
| NEWS2 score of 5 or 6 | Medium |

| | |
|---|---|
| NEWS2 score of 7 or more | High |

If a patient meets the criteria for more than one category the worst category will be selected.

### 5.3.3 Derivation of Duration of Symptoms at Baseline

Duration of symptoms at baseline, which will be considered for subgrouping, will be calculated as date of randomisation – date of initial COVID-19 symptoms + 1.

### 5.3.4 Derivation of EQ-5D-5L Index Values

Index values will be calculated for patients in the home setting from their EQ-5D-5L profiles using the method proposed by van Hout B, Janssen MF et al [2], as described below.

The EQ-5D-5L profile for an individual is found by combining the scores from each of the five dimensions to form a five-digit number in the following order: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is graded with a score between 1 and 5 where 1 indicates no problems and 5 indicates unable to/extreme problems. Therefore, a patient with no problems in any of the five dimensions will have a profile 11111 and a patient with no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression will have a profile of 12345.

Each profile score is used to calculate an index value for the country of residence. Index values can be a maximum of 1 and a higher index value indicates a better quality of life, e.g. someone with a profile of 11111, indicating no problems would have an index value of 1.000.

The crosswalk value sets found on the EuroQol website: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/.

Because this international study includes a number of countries where a crosswalk index is not available the UK crosswalk index will be used for all patients. To help interpret quality of life internationally the Level Sum Score (LSS) will also be calculated as proposed in Feng et al 2021 [10]. The LSS is calculated by assigning a numerical value to each response level (i.e., 1 for “no problems”, 5 for “extreme problems”/”unable to”) and summing these values across the five items, resulting in a score from 5 (11111, no problems on any dimension) to 25 (55555, extreme problems on all dimensions) for the EQ-5D-5L.

### 5.3.5 Derivation of the General Anxiety Disorder-7 Total Score

General Anxiety Disorder-7 (GAD-7) scores seven individual item scales by assigning scores of 0, 1, 2, and 3, to the response categories of “not at all”, “several days”, “more than half the days”, and “nearly every day”, respectively. The GAD-7 total score is calculated using the method described in the instruction manual [3], by summing the individual item scales to give a total score between 0 and 21. If any of the individual item scores are missing the total score will not be calculated.

Total aggregated score will be used to categorise severity of generalised anxiety disorder as per table 2.

**Table 2: Anxiety severity categories for GAD-7 total score**

| GAD-7 Total Score Range | Anxiety Severity |
|---|---|
| 0 – 4 | None/Minimal |
| 5 – 9 | Mild |
| 10 – 14 | Moderate |
| 15 – 21 | Severe |

### 5.3.6 Derivation of the Patient Health Questionnaire-9 Total Score

Patient Health Questionnaire-9 (PHQ-9) scores nine individual item scales by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all", "several days", "more than half the days", and "nearly every day", respectively. PHQ-9 total scores are calculated using the method described in the instruction manual [3], by summing the individual item scales to give a total score between 0 and 27. If any of the individual item scores are missing the total score will not be calculated.

Total aggregated score will be used to categorise severity of depression as per table 3.

**Table 3: Depression severity categories for PHQ-9 total score**

| PHQ-9 Total Score Range | Depression Severity |
|---|---|
| 0 – 4 | None/Minimal |
| 5 – 9 | Mild |
| 10 – 14 | Moderate |
| 15 – 19 | Moderately Severe |
| 20 – 27 | Severe |

### 5.3.7 Derivation Functional Assessment of Chronic Illness Therapy Fatigue Scale Total Score

Total scores from version 4 of the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale can be calculated using the following algorithm, as per the scoring guidelines [4]:

- If less than 50% of the items have been completed total score should not be calculated.
- Otherwise, the item scores should be reversed, as 4 – Item score, for all items except the questions "I have energy" and "I am able to do my usual activities".
- Sum the converted values.
- Multiply the summed values by the total number of items on the scale (13) and divide by the number of answered items.

This algorithm will give total score on a scale between 0 and 52, where a higher total score indicates lower level of fatigue.

### 5.3.8 Derivation of the Brief Pain Inventory Composite Scores

Overall pain severity score will be calculated as the mean of questions 3 to 6 of the brief pain inventory short form. If any of questions 3 to 6 are unanswered the overall pain severity score should not be calculated.

The pain interference score is calculated as the mean of the scales under question 9 of the brief pain inventory. The pain interference score can be calculated provided at least 4 of the 7 interference scales have been completed, otherwise the pain interference score should be missing.

Both of the above measures are as defined in the brief pain inventory user guide [5].

### 5.3.9 Derivation of Oxygen Variables

The fraction of inhaled oxygen ($FiO_2$) can be calculated from the given oxygen flow in L/min using Table 4 below for all devices except the Venturi masks [12].

**Table 4: Calculation of $FiO_2$ for all Devices except Venturi Masks**

| Flow (L/min) | $FiO_2$ |
|---|---|
| 1 | 0.28 |
| 2 | 0.38 |
| 3 | 0.43 |
| 4 | 0.50 |
| 5 | 0.56 |
| 6 | 0.62 |
| 7 | 0.64 |
| 8 | 0.66 |
| 9 | 0.71 |
| 10 | 0.73 |
| 11 | 0.75 |
| 12 | 0.76 |
| 13 | 0.77 |
| 14 | 0.79 |
| 15 | 0.81 |

Oxygen flow should be taken from the Vital Signs page of the CRF. Any oxygen flow records which are expressed as decimals should be rounded up to the nearest integer. For any oxygen flow records expressed as a range the maximum value should be taken to calculate $FiO_2$.

For Venturi masks the oxygen flow should be presented in the raw data as $FiO_2$. However of the oxygen flow is presented in L/min the standard Venturi mask conversion should be used as per Table 5.

**Table 5: Calculation of $FiO_2$ for Venturi Masks**

| Flow (L/min) | $FiO_2$ |
|---|---|
| 2 | 0.24 |
| 4 | 0.28 |
| 6 | 0.31 |
| 8 | 0.35 |
| 10 | 0.40 |
| 15 | 0.60 |

Any oxygen flow volume which does not appear in the above table should be rounded up to the closest volume available.

For summary statistics $FiO_2$ should be expressed as a percentage.

The Saturated Oxygen ($SpO_2$) / $FiO_2$ ratio is calculated as the $SpO_2$ (expressed as a decimal) / $FiO_2$ at the corresponding visit.

## 6 Sample Size

A sample size of 610 subjects in total using a 1:1 randomisation ratio (305 subjects per treatment arm) has been chosen to provide at least 90% power to detect a hazard ratio of 1.45 in time to hospital discharge and a hazard ratio of 1.7 in time to recovery and at least 95% power to declare statistical significance on at least one of the primary endpoints. This sample size has been calculated using a global 2-sided alpha level of 0.05 and adjusting for the Hochberg procedure to allow for multiple comparisons. This sample size also allows for an interim analysis to assess futility after the first 300 randomised subjects (150 subjects per treatment arm) have completed the Day 35 assessment or have withdrawn from the study. The futility analysis is planned to be non-binding.

The power of the study was confirmed via simulation as follows:

Time to recovery and time to discharge in the placebo subjects were drawn from exponential distributions with rate parameters:

$$Placebo\ Time\ to\ Sustained\ Recovery \sim Exp\left(\frac{log\left(\frac{100}{70}\right)}{28}\right) \text{ and}$$

$$Placebo\ Time\ to\ Sustained\ Discharge \sim Exp\left(\frac{log\left(\frac{100}{30}\right)}{28}\right)$$

In the simulations, this gives the placebo arm:

- a median time to recovery (50% recovery) of approximately 54.4 days and a 30% recovery at exactly 28 days

- a median time to discharge (50% discharge) of approximately 16.1 days and a 70% discharge at exactly 28 days

Assumed hazard ratios (SNG vs Placebo) for recovery and discharge of 1.35 and 1.7 respectively, this data can be simulated:

$$Active\ Time\ to\ Sustained\ Recovery \sim Exp\left(\frac{log\left(\frac{100}{70}\right)}{28*1.35}\right) \text{ and}$$

$$Active\ Time\ to\ Sustained\ Discharge \sim Exp\left(\frac{log\left(\frac{100}{30}\right)}{28 * 1.7}\right)$$

This gives the active arm:

- a median time to recovery (50% recovery) of approximately 40.3 days and a 30% recovery at approximately 21.5 days
- a median time to discharge (50% discharge) of approximately 9.5 days and a 70% discharge at approximately 16.5 days

It was additionally assumed that study withdrawal followed an exponential distribution on both treatment arms

$$Withdrawal\ From\ Study \sim \min\left(Exp\left(\frac{log\left(\frac{100}{75}\right)}{28}\right), 28\right)$$

so that in the simulations, on average 25% of patients withdraw early from the study (i.e. before Day 35), and the other 75% have complete follow-up.

All patients were assumed to contribute to the primary endpoints up to their withdrawal from the study, thus patients who withdrew may still meet one or both primary endpoints. Patients who withdrew early without meeting the primary endpoint(s) were censored in the simulation analyses. All patients were administratively censored at the last time point (on Day 28).

An interim analysis at which both primary endpoints were assessed was simulated using the data from the first 300 randomised subjects (150 on each treatment arm). The simulated study was stopped for futility if the Z statistic (calculated as the partial likelihood log hazard ratio for SNG vs Placebo divided by its standard error) for both primary analyses was less than 1.4. Otherwise the simulated study continued to recruit the remaining 310 subjects (155 on each treatment arm) and the pooled (pre-interim and post-interim) simulated data was analysed at the final analysis.

The power of the overall study to meet both primary endpoints was simulated as over 90%. The power to meet at least one primary endpoint was approximately 95%.

In the case of the complete absence of efficacy in one of the primary endpoints the power to meet the other primary endpoint was approximately 85%.

Additional simulations were performed in which a statistical dependency was created between the two primary endpoints while maintaining the same marginal distributions. The power to show statistical significance in at either endpoint was maintained but the power to reach statistical significance in both primary endpoints was (as expected) slightly increased.

For further information refer to the simulation report in Appendix II.

# 7 General Considerations

## 7.1 Analysis Populations

### 7.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) analysis population will include all randomised patients. The ITT population will be the primary analysis population for efficacy analyses and will summarise patients by their randomised treatment group.

### 7.1.2 Per Protocol Population

The Per Protocol (PP) analysis population will include all patients within the ITT population who do not have any protocol deviations with an impact on efficacy on or prior to Day 35 and will be used for supportive analyses of efficacy endpoints, as appropriate. Relevant protocol deviations may include, but are not limited to the following:

- Patient was not admitted to hospital due to the severity of their COVID-19.
- Patient did not have a positive RT-PCR virus test by RT-PCR at screening. Evidence of ongoing SARS-CoV-2 infection for more than 3 weeks, confirmed by a validated molecular assay or validated antigen assay.
- OSCI score at baseline was ≠ 4.
- Patient is receiving mechanical ventilation or is in intensive care prior to randomisation.
- Patient could not use a nebuliser with a mouthpiece at baseline.
- Patient failed to receive at least two full doses of the scheduled doses in the first 3 days after randomisation.
- No post baseline OSCI assessments were performed.
- Patient was not discharged from hospital for reasons other than the severity of their condition.

Blinded protocol deviation data will be reviewed routinely in accordance with the protocol deviation plan. Decisions regarding the exclusion of patients from the PP population who have completed the day 35 assessments or who have withdrawn from the study and have all data available and no outstanding data queries will be made during these meetings. Following completion of the study database the status of all patients with regards to the PP population will be reviewed and confirmed.

Following study unblinding, the randomisation schedule will be used to confirm if the randomised drug was correctly administered at each assessment by comparing the syringe numbers entered into the database against the syringe numbers in the material lists. Patients randomised to SNG001 will be excluded from the PP population if SNG001 was administered on less than 2 occasions in the first 3 days of treatment (either missed doses or incorrectly treated with placebo). For patients randomised to Placebo,

assessments of OSCI, BCSS, NEWS2 and EQ-5D-5L conducted on or after the first dose of SNG001 will be excluded from analyses of the PP population.

### 7.1.3 Safety Population

The Safety analysis population will include all patients in the ITT population who receive at least one dose of study drug. Subjects within the Safety population will be summarised under the treatment they actually received. The treatment received will be identified by merging the randomisation schedule with the study drug administration page of the Case Report Form (CRF) by the IMP box number, if available. Any patients who receive SNG001 at any time will be summarised under the SNG001 treatment arm. Patients who receive placebo for every dose will be summarised under the placebo treatment arm. The safety population will be used for analysis and summaries of safety endpoints.

CCI [redacted]
CCI [redacted]

### 7.1.5 Immunogenicity Population

The Immunogenicity Population will include patients enrolled at sites where immunogenicity sample collection was feasible and who have at least one valid immunogenicity result.

## 7.2 Covariates and Subgroups

The variables below have been selected because they are probable risk factors relating to severity and recovery from SARS-CoV-2.

The following subgroups will be analysed:

- Age category:
  - < Median age
  - ≥ Median age
  - <40
  - 40 - 49
  - 50 - 65
  - 66 - 75
  - >75
- Co-morbid conditions at screening of cancer, cerebrovascular disease, chronic kidney disease, chronic lung diseases, chronic liver disease, diabetes mellitus type 1 and type 2, heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies), mental health disorders or tuberculosis. These comorbidities are listed by the Centres for Disease Control and Prevention [11] as supported by at least one meta-analysis or systematic review. Obesity and smoking are also listed as comorbidities, however these are covered by other subgroups listed below.
  - Does not have comorbidity at screening.
  - Has one comorbidity at screening

  - Has more than one comorbidity at screening
- Current smoking status:
  - Current smoker
  - Current e-cig user
  - Former smoker
  - Does not smoke
- Sex:
  - Male
  - Female
- BMI category:
  - < 30
  - ≥ 30
- Race:
  - White
  - Non-White
- Prior duration of symptoms (in days):
  - < Median duration
  - ≥ Median duration
  - ≤ 7
  - > 7

- Geographic region (See Section 7.5)
- Breathlessness at Baseline
  - 4
  - < 4
  - ≥ 3
  - <3
  - ≥ 2
  - < 2

- COVID-19 vaccine status at randomisation:
  - No prior COVID-19 vaccination
  - Partially vaccinated
  - Fully vaccinated (two doses received for vaccines required to be double dosed, or one dose received for vaccines required to be a single dose [e.g. Janssen/Johnson and Johnson vaccine]).

- S/F Ratio at randomisation will be categorised as 'Low', 'Medium' or 'High'. There is no agreed definition for these classifications, therefore the categorisation will be data driven and defined using percentiles:
  - Low (≤ 33$^{rd}$ percentile)
  - Medium (> 33$^{rd}$ percentile to ≤ 66$^{th}$ percentile)

- High (> 66th percentile)

The following variables are factors of interest which have been selected so show homogeneity of the treatment effect:

- COVID-19 Related Therapy at randomisation
  - Remdesivir by any route
  - Corticosteroids by any systemic route (Dexamethasone, Methylprednisolone, Prednisolone, Hydrocortisone)
  - Dexamethasone by any route
  - Dexamethasone administered orally
  - Dexamethasone administered intravenously

  All cases of the above medication use will be included, regardless of whether indicated for COVID-19 or a comorbidity.

- SNG001 Manufacturing Batch
  - SNG001 manufactured using CCI derived material
  - SNG001 manufactured using CCI derived material.

The following covariates will be included in statistical models:

- Age as a continuous variable
- Sex:
  - Male
  - Female
- Prior duration of symptoms as a continuous variable
- Geographic region (See Section 7.5)
- COVID-19 vaccine status at randomisation:
  - No prior COVID-19 vaccination
  - Partially vaccinated
  - Fully vaccinated

Patients who receive different types of COVID-19 vaccination will be pooled into a single subgroup.

Only subgroups with at least 20 patients in total will be included in any summaries or analyses.

For analyses of change from baseline for variables other than OSCI the baseline value will also be included as a covariate.

For subgroup analyses the subgroup variable will not be included in the models. The study has not been powered for any of the subgroups defined above, therefore all subgroup analyses should be considered exploratory.

## 7.3 Missing Data

### 7.3.1 OSCI

#### *7.3.1.1 General Imputation Rules*

For analyses using the OSCI, including the primary and key secondary endpoints, subjects with an OSCI score of 8, indicating death, will have any subsequent missing OSCI assessments set as 8. In addition, if other data sources such as AEs indicate a patient has died all missing OSCI scores on and after the date of death will be set as 8. Any missing baseline OSCI scores will be imputed as 4, as per the study inclusion criteria.

#### *7.3.1.2 Imputation Rules for Time to Event Derived Endpoints*

Primary analyses of time to hospital discharge and time to recovery will use a censoring approach for missing OSCI data for patients who discontinue the study prior to hospital discharge or recovery. I.e. patients who discontinue the study prior to hospital discharge or recovery and prior to day 28 will be censored at the date of their last OSCI assessment. However, this assumption of independent censoring will be tested in sensitivity analyses by multiple imputation of the time to hospital discharge and time to recovery. Further details are given in Section 9.1.1.3.

#### *7.3.1.3 Imputation Rules for Binary Endpoints*

Key secondary analyses will use the available data. Therefore, for subjects who withdraw from the study prior to day 35 this assumes that any progression to severe disease, intubation or death can only occur prior to study withdrawal. This assumption will be tested by using multiple imputation methods to impute the missing data. Further details are given in Section 9.2.1.3.

### 7.3.2 BCSS

Missing breathlessness scores will be imputed according to the OSCI score at the corresponding date of assessment. If the OSCI score ≥ 5 at the same assessment as the missing breathlessness score then the breathlessness score will be imputed as 4 (the maximum breathlessness). At all other assessments breathlessness will be assumed Missing at Random (MAR). Missing cough and sputum scores will be assumed MAR at all days. MAR assessments will not be explicitly imputed but will be assessed as such by the analysis method. For the calculation of total BCSS score at days where breathlessness has been imputed as 4, the cough and sputum scores from the last observed days will not be imputed if missing and therefore the total BCSS score will be missing at these days.

### 7.3.3 Partial Dates

For adverse events, partial dates will only be imputed for the purposes of determining treatment emergence. The following rules will be applied:

- If only the AE start day is missing and the AE start month is on or after the month of first dose then the AE will be considered treatment emergent.
- If the AE start day and month are missing and the AE start year is on or after the year of first dose, then the AE will be considered treatment emergent.

- If the AE start date is completely missing, then the AE will be considered treatment emergent.

Due to the requirement that dosing is started within 24 hours of consent AE end dates will not be taken into consideration.

For medications, partial end dates will be imputed only to determine medication categorisation as prior or concomitant. If the end date is missing the medication will be assumed concomitant. Otherwise, partial end dates will be imputed as the latest possible date (last day of the month if the day is missing or 31st December if the day and month are missing). If the imputed date is after the first dose date the medication will be assumed concomitant.

## 7.4 Interim Analyses and Data Monitoring

### 7.4.1 Purpose of Interim Analyses

Two types of interim analysis will be used during the trial:

- DSMC meetings for the purpose of ongoing review of safety data.
- An interim analysis of unblinded efficacy data to allow for early stopping of the trial due to futility will be conducted if it is feasible for the interim data to be analysed and interpreted within a timeframe which is ethical and of scientific value to the study.

In addition, a primary analysis will be conducted once all patients have completed their day 35 assessment or have withdrawn from the study (i.e. once all data required for the evaluation of the primary and secondary endpoints has been entered into the clinical study database and that data has been locked). This analysis will be conducted by the main statistical team, who will be fully unblinded at the point of database lock.

### 7.4.2 Planned Schedule of Interim Analyses

The first DSMC meeting will occur prior to the 100th patient completing study treatment. Further DSMC meetings will be organised as required or as requested by the DSMC. For further details refer to the DSMC charter.

The interim analysis for futility will occur after the first 300 randomised patients have completed day 35 or have withdrawn from the study if it is feasible for the interim data to be analysed and interpreted within a timeframe which is ethical and of scientific value to the study.

### 7.4.3 Scope of Adaptations

As per the DSMC charter the DSMC may provide recommendations about necessary changes to the study protocol and also whether to stop or continue the study.

Regarding the interim analysis for futility, non-binding futility rules will be documented in the Independent Data Monitoring Committee (IDMC) charter. Following the futility analysis, the IDMC will meet to review the unblinded data and will make a recommendation to either continue the study or to stop the study due to futility. The IDMC may also recommend stopping the study due to safety concerns or due to evidence of

a paradoxical treatment effect between recovery/discharge and disease progression or death regardless of success versus the futility criteria. No sample size adjustments are planned.

#### 7.4.4 Adjustment of Confidence Intervals and p-values

The interim analysis will be used to assess futility only. The trial will not be stopped due to efficacy. Therefore, no alpha adjustment is required for the inclusion of the interim analysis and the global alpha of 0.05 will be preserved for the final analysis.

#### 7.4.5 Practical Measures to Minimise Bias

As per the DSMC charter version 2, unblinded outputs will be provided from the second DSMC meeting onwards. An independent statistical team will generate unblinded outputs and those results will be shared with unblinded team members only. In addition, an independent statistician who will have no input to the study conduct post unblinding will attend the DSMC closed sessions. The unblinded statistical team will have no input to the study conduct post unblinding and will not be involved in the programming or generation of blinded outputs post unblinding.

The interim analysis for futility will be produced by an independent statistical team who will have no input to the study conduct post unblinding and will not be involved in the programming or generation of blinded outputs post unblinding. Unblinded results will be shared with unblinded team members only. The recommendation to continue or stop the study will be guided by pre-defined criteria documented in the DSMC charter.

The main statistical team will be fully unblinded at the point of the primary analysis database lock. However, it is expected this will occur prior to the completion of all follow-up assessments. Therefore, to ensure these uncompleted assessments are not biased by knowledge of the randomised treatment to individual subjects, unblinded outputs will be released to the unblinded team at an aggregate level only. Individual randomisation assignments may be released to study team members who will have no further input into the study conduct, where required for decision making. Any changes to the planned analysis following unblinding for the primary analysis will be documented as such in the Clinical Study Report (CSR).

Full details will be documented in an unblinding plan.

#### 7.4.6 Documentation of Interim Analyses

A snapshot of the data, programs, Study Data Tabulation Model (SDTM) and ADaM datasets and outputs for DSMC and IDMC meetings and the primary analysis will be archived at the point of delivery and included in the blinded/unblinded study master file (SMF) and trial master file (TMF), as appropriate.

### 7.5 Multi-centre Studies

This study will be conducted by multiple investigators at multiple centres internationally. Randomisation to treatment arms is stratified by centre. When specified, statistical analysis will be adjusted for geographic region. Geographic region will be categorised as per table 4. If not many patients are recruited in the sites of the Latin American region resulting in analytical issues such as non-convergence, Latin

America patients may be combined with those of India for some or all planned covariate adjusted analyses.

**Table 4: Geographic regions for the purpose of analysis**

| Geographic Region | Country |
|---|---|
| Latin America | Argentina, Brazil, Colombia, Mexico |
| Europe and USA | Belgium, France, Germany, Israel, Italy, Netherlands, Portugal, Romania, Serbia, Spain, United Kingdom, United States of America |
| India | India |

### 7.6 Multiple Testing

A Hochberg procedure will be used to test the primary endpoints. Therefore, if the two-sided p-value for the estimate of time to hospital discharge is below 0.05 and the two-sided p-value for the estimate of time to recovery is below 0.05 the null hypotheses for both endpoints will be rejected. Otherwise, if the smallest of the two-sided p-values is below 0.025 only the null hypothesis associated with the smallest p-value will be rejected. In any other circumstance neither null hypothesis will be rejected.

The first key secondary endpoint will be formally tested using a two-sided alpha of 0.05 only if both primary endpoints are statistically significant. The second and third key secondary endpoints will be formally tested, in sequence, using a two-sided alpha of 0.05 only if all prior hypothesis tests are statistically significant.

## 8 Summary of Study Data

In general, continuous variables will be summarised through descriptive statistics, including the number of subjects, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarised as frequencies and percentages. All summary tables will be structured with a column for each treatment in the order (Placebo, SNG001) and will be annotated with the total population size relevant to that table/treatment, including any missing observations. A total column, including all subjects within the analysis population will be included for study population tables only.

All available and relevant study data will be listed. All safety and study drug exposure data will be listed using the Safety population, PK concentrations and parameters will be listed using the PK population, immunogenicity results will be listed using the Immunogenicity population and all other data will be listed using the ITT population.

### 8.1 Subject Disposition

The number and percentage of subjects belonging to the following categories will be presented for the ITT population:

- ITT analysis population
- PP analysis population

- Safety analysis population (summarised under actual treatment arm).
- Treatment status
    - Was not treated
    - Completed treatment
    - Discontinued treatment
    - Principal reason for premature treatment discontinuation.
- Study status
    - Completed study
    - Ongoing (in treatment phase, in short term follow-up [Day 15 – Day 35], In long term follow-up [after Day 35] – all categories to be included for the purposes of DSMC meetings and the interim analysis, just an 'Ongoing – after Day 35' category will be included for the primary analysis and to be removed completely for the final analysis).
    - Discontinued from the study
        - At any time
        - Day 1 – Day 14
        - Day 15 – Day 35
        - Day 36 – Day 90
        - Principal reason for premature study withdrawal.

Study discontinuation will be plotted by treatment using mosaic plots for the patients discontinued based on the above defined visit periods.

### 8.2 Protocol Deviations

Important protocol deviations will be summarised for the ITT population. The number and percentage of patients with at least one important protocol deviation will be presented as well as the number and percentage of patients with at least one protocol deviation within each protocol deviation category and subcategory, overall and by country and site.

### 8.3 Demographic and Baseline Variables

The following demographic and baseline information will be summarised for the ITT population. Data collected at the Day 0/ Day 1 visit will be used, unless otherwise indicated below.

- Age
- Sex
- Race
- Ethnic origin
- Care home residence (yes, no)
- Height, weight and BMI at screening.
- Presence of selected co-morbidities (hypertension, cardiovascular disease (excluding hypertension), diabetes, a chronic lung condition or cancer).
- Number of distinct co-morbidities (0, 1, 2, 3+).
- Smoking status (never smoked, former smoker, current tobacco user, current e-cig user).
- Duration of symptoms at baseline.

The summary of demographic and baseline information will be repeated for each of the subgroups defined in Section 7.2. The number and percentage of patients within each subgroup will also be summarised.

A summary of oxygen use at randomisation will also be presented. Summary statistics will be presented for the baseline percentage FiO2, the baseline percentage oxygen saturation and the baseline S/F ratio.

### 8.4 Medical History

Medical history will be coded using the version 23 of the Medical Dictionary for Regulatory Activities (MedDRA).

Medical history will be summarised for the ITT population by System Organ Class (SOC) and Preferred Term (PT). Summary tables will contain the number and percentage of patients. A patient who has multiple conditions in the same SOC or with the same PT will be counted only once in the patient counts. Medical history summaries will be sorted by the internationally agreed SOC order (Appendix III) and decreasing frequency of PT within SOC in the total column.

SARS-CoV-2 infection history at screening will be summarised for the ITT population. The number and percentage of patients experiencing each symptom of COVID-19 on admission to hospital will be displayed. In addition, the number and percentage of patients with each COVID-19 variant will be presented, where data are available.

The number and percentage of patients with comorbidities will be summarised by the comorbidity groups defined in Section 7.2 and preferred term. Preferred terms falling under each comorbidity group will be identified by a blinded medical review of the study data.

### 8.5 Medications

Medications will be coded according to the 2009 version of the World Health Organisation Drug Dictionary (WHODD) combined with the online 2020 version.

Medications will be defined as prior or concomitant in the hospital setting and prior, concomitant or post study treatment in the home setting. Prior and concomitant medications will be summarised for the ITT population by Anatomical Therapeutic Chemical (ATC) class level 3 and preferred drug name, where;

- ‘Prior’ medications are medications which started and stopped prior to the first dose of study drug.
- ‘Concomitant’ medications are medications which started prior to, on or after the first dose of study drug and up to 24 hours after the last dose of study drug and ended on or after the date of first dose of study drug or were ongoing at the end of the study.
- ‘Post study treatment’ medications will be defined as medications which were started more than 24 hours after the last dose of study treatment.

See Section 7.3.3 for handling of partial dates for medications. In cases where it is not possible to define a medication as prior or concomitant the medication will be classified by the worst case; i.e. concomitant.

Concomitant and post study treatment medications which are used for direct treatment of COVID-19 will be summarised, including the number and percentage of subjects receiving such treatment, broken down by treatment name. Medications used for treatment of COVID-19 will be identified by a blinded medical review of the study data.

COVID-19 vaccinations prior to study enrolment will be summarised, including the number and percentage of vaccinated subjects, the type of vaccine received, whether a single dose or double dose vaccine was received, whether the same vaccine was received for both doses and the time since each vaccination dose. Post randomisation COVID-19 vaccinations will also be summarised, including the number and percentage of non-vaccinated and vaccinated patients as well as the patients with the first dose pre-randomisation and second dose in follow-up period.

### 8.6 Treatment Compliance

Percentage treatment compliance will be summarised for the Safety population.

Treatment compliance is calculated as total number of received doses/ total number of scheduled doses x 100, where the total number of scheduled doses only includes doses prior to study withdrawal.

Percentage treatment compliance will be summarised through descriptive statistics and the number and percentage of patients with < 80%, 80% - <100% and 100% compliance will be presented.

Treatment compliance will also be summarised as the number and percentage of patients that missed dose due to:

- OSCI score of 5 or above
- Other reasons

The number of patients who received partially administered doses will also be summarised alongside the reason for partial administration.

### 8.7 Treatment Exposure

The duration of exposure and number of doses administered will be summarised for the Safety population. The duration of exposure is calculated as the number of days between first dose and last dose (inclusive), regardless of any missed doses. The number of doses administered will be summarised in the form of cumulative frequencies showing the number and percentage of patients receiving ≥ 1 dose, ≥ 2 doses, ≥ 3 doses etc., up to 14 doses. The number of doses missed will also be summarised. In addition, the number and percentage of patients fulfilling the study drug exposure criteria for the PP population (i.e. patients who receive at least two doses in the first 3 days) will be summarised.

## 9 Efficacy Analyses

All efficacy analyses and summaries described in this section will use the ITT population. Some efficacy analyses will be repeated for other populations and for the subgroups defined in Section 7.2 as per table 7 below.

**Table 7: Planned efficacy analyses**

| Planned Analysis | Population | | |
|---|---|---|---|
| | ITT | PP | Subgroups of the ITT |
| Cox proportional hazards analysis of time to hospital discharge | X | X | X[1] |
| Cox proportional hazards analysis of time to recovery | X | X | X[1] |
| Kaplan Meier analysis of time to hospital discharge | X | X | X[1] |
| Kaplan Meier analysis of time to recovery | X | X | X[1] |
| Logistic regression analysis of severe disease or death within 35 days of first dose | X | X | X[1] |
| Logistic regression analysis of intubation or death within 35 days of first dose | X | X | X[1] |
| Logistic regression analysis of death within 35 days of first dose | X | X | |
| Logistic regression analysis of recovery at days 7, 14, 21 and 28 | X | X | |
| Logistic regression analysis of hospital discharge at days 7, 14, 21 and 28 | X | X | |
| Proportional odds analysis of improvement on the OSCI scale at days 7, 14, 21 and 28 | X | X | X |
| Mixed model for repeated measures (MMRM) analysis of BCSS total score | X | | |
| MMRM analysis for breathlessness and cough scores | X | X | X |

[1] Analysis will only be performed if sufficient events occur within the analysed population.

## 9.1 Primary Efficacy Endpoints

### 9.1.1 Time to Hospital Discharge

#### *9.1.1.1 Primary Estimand*

The primary estimand will be the hazard ratio of SNG001 versus placebo for the time to hospital discharge of patients in the ITT population. Intercurrent events will be handled as per table 8.

**Table 8: Intercurrent events and policies for the primary estimand of time to hospital discharge**

| Intercurrent event | Policy |
|---|---|
| Death | Composite variable: Patients who die on or prior to Day 28 will have time to hospital discharge right censored at 28 days (the maximum time to discharge). |
| Premature treatment discontinuation and missed doses | Treatment policy: The time to hospital discharge will be used regardless of treatment discontinuation and the number of missed doses. |
| Withdrawal from study following hospital discharge | Hypothetical: The time to hospital discharge will be used regardless of study withdrawal where discharge was sustained for 7 days. Otherwise, patients will be censored at the last date known to be hospitalised for patients who withdrew during the 7 day rebound period. This approach has been proposed because discontinuation during the rebound period is expected to be due to lack of interest/lack |

| | |
|---|---|
| | of motivation/lack of time to continue participating in the study rather than relapse. |
| Withdrawal from study prior to hospital discharge | While-on-study: Time to hospital discharge will be right censored at the time of withdrawal from the study or at 28 days, whichever occurs first. The evaluation period for this endpoint is 28 days, therefore estimating the time to hospital discharge after Day 28 would not be appropriate. Premature study withdrawal is expected to be independent to the treatment effect, therefore a censoring approach in this scenario is considered appropriate. However, this assumption will be tested by appropriate sensitivity analyses. |
| Other protocol deviations and concomitant medications affecting efficacy | Treatment policy: Time to hospital discharge will be used regardless of any concomitant medication use or protocol deviations. |

#### *9.1.1.2 Primary Analysis of the Primary Estimand*

The primary analysis of time to hospital discharge will be a Cox proportional hazards model with time to hospital discharge calculated according to Section 5.3.1.1.

Covariates will be included in the proportional hazards model as per Section 7.2.

The hazard ratio for hospital discharge of SNG001 versus placebo, 95% confidence intervals (CI) and p-value will be presented. In addition, unadjusted quartile estimates will be calculated through the Kaplan-Meier method with 95% CI calculated by the Brookmeyer-Crowley method.

Ties in event times will be handled using the exact method, or the Efron approximation if computational difficulties arise. Schoenfeld residuals will be plotted to assess the proportional hazards assumption.

The Restricted Mean Survival Time (RMST) will also be presented.

The statistical significance of the primary analysis of time to hospital discharge will be formally assessed by the Hochberg procedure, as detailed in Section 7.6, and a statistically significant p-value according to the multiple testing strategy will be indicated in the output.

The hazard ratios for hospital discharge and for recovery in SNG001 versus placebo and their corresponding 95% CI and p-values will be presented in a forest plot, in which the x-axis will represent the hazard ratio and the y-axis will stand for the estimates of the two co-primary endpoints.

The proportion (%) of patients who were discharged from hospital on or before visit up to Day 28 will be presented in a table alongside the probability of survival calculated from a Kaplan-Meier analysis and Greenwood 95% confidence intervals. Plots will be produced of Kaplan-Meier estimates over time and the proportion (%) of patients who were discharged from hospital on or before visit up to Day 28 for SNG001 versus placebo.

#### *9.1.1.3 Sensitivity Analyses of the Primary Estimand*

The sensitivity of the primary analysis to missing data due to withdrawal from study prior to hospital discharge/ recovery will be assessed through a tipping point analysis, where missing data will be imputed

as described by Jackson et al [6]. To perform the multiple imputation M datasets will first be created through bootstrapping. The bootstrapping will be applied independently for each treatment group (a treatment stratified bootstrap). Each created dataset will therefore contain $n_1$ Placebo patients and $n_2$ SNG001 patients where $n_1$ and $n_2$ are the number of patients randomised to Placebo and SNG001 respectively. The primary analysis method will be used to assess each of the bootstrapped datasets to generate estimates of the model coefficients within each dataset. The vector of model coefficients can be written algebraically for the j[th] dataset as $\beta_j^*$ and the vector of covariates values for the i[th] patient as $Z_i$.

Missing hospital discharge and recovery times for patients censored prior to day 28 will be estimated as $min(T_{ij} = C_i + A_{ij}, 28)$, where $T_{ij}$ is the imputed time to discharge/recovery in the j[th] dataset for the i[th] patient, $C_i$ is the observed censored time and $A_{ij}$ is the simulated time between censoring and the time to event. A maximum constraint of 28 days is applied to the imputed times because the rate and time to hospital discharge and recovery beyond this time cannot be assessed due to the limitations of the study design. $A_{ij}$ will be estimated using the Bender et al method [7], by the following calculation:

$$A_{ij} = H_{A_{ij}}^{-1}\left[-log(U_{ij})exp(-\beta_j^* Z_i - \gamma_i)\right],$$

where $U_{ij}$ is randomly generated from a Uniform(0,1) distribution, $H_{A_{ij}}^{-1}$ is the inverse cumulative baseline hazard function for $A_{ij}$ and $\gamma_i$ is a sensitivity parameter. If $\gamma_i$ is set to 0 this will represent a Missing at Random (MAR) approach, if $\gamma_i$ < 0 the time to discharge/recovery will occur earlier than that of the MAR approach and if $\gamma_i$ > 0 discharge/recovery will occur later than that of the MAR approach. Values of $\gamma$ will be varied independently for each treatment group.

The M imputed datasets will be analysed using the primary analysis model and the M estimates will be combined with Rubin's variance formula.

The value of M will be chosen large enough such that the choice of the seed used in sampling functions has a negligible impact on estimates.

For each imputed dataset and for each value of $\gamma_i$ the primary analysis method will be repeated. The estimates from the imputed datasets will be combined for each value of $\gamma_i$ using Rubin's rules [8]. The results for the different combinations of $\gamma_i$ for Placebo and SNG001 patients will be plotted on a heat map to identify, if applicable, where the p-values becomes non-significant. This 'tipping point' will also be tabulated along with specific values of $\gamma_i$ on the exponentiated scale.

A jump to reference Missing Not at Random (MNAR) data imputation will also be performed using similar a method, but only assuming all patients who withdraw early follow the same pattern as patients who are randomised to placebo. $\gamma_i$ will be set to 0 for this imputation.

These sensitivity analyses will assess the robustness of the results to a departure from the censored at random assumption of a Cox proportional hazards model. To aid interpretation the average proportion of patients who were discharged from hospital will be presented alongside the average difference in the restricted mean survival time.

An additional sensitivity analysis will assess hospital discharge that has been sustained for 7 days. In this analysis patients will be considered as discharged from hospital if they are not re-admitted to hospital within 7 days of hospital discharge. This analysis will evaluate the the primary endpoint using the same rebound assessment period for all patients .

The primary estimand will be further evaluated for each of the subgroups described in Section 7.2. The analysis method for the primary endpoint described in Section 9.1.1.2 will be used to evaluate each subgroup.

#### *9.1.1.4 Supportive Estimands*

A supportive estimand of the primary endpoint will estimate the hazard ratio of SNG001 versus placebo for the time to hospital discharge of patients in the per protocol population. Reasons for excluding patients from the PP population are described in Section 7.1.2. Of note, many of the reasons are based on assessments prior to randomisation and treatment and so the exclusions are independent of treatment. Intercurrent events will be handled as per table 9.

**Table 9: Intercurrent events and policies for the supportive estimand of time to hospital discharge**

| Intercurrent event | Policy |
|---|---|
| Death | Composite variable: Patients who die during the study period will have time to hospital discharge right censored at 28 days (the maximum time to discharge). |
| Missed 2 of the first 3 scheduled doses | Hypothetical (estimand for a situation with treatment compliance): The time to hospital discharge will be considered missing if two or more doses of the randomised treatment were missed within the first three days of therapy, with the corresponding patients excluded from the PP analysis set. A single dose within the first three scheduled dosing days is not expected to be sufficient for the study drug to be effective, therefore this approach will help establish the true treatment effect. It is assumed that such exclusions are not related to treatment. |
| Other premature treatment discontinuation and missed doses | Treatment policy: The time to hospital discharge will be used regardless of treatment discontinuation and the number of missed doses (other than missing 2 out of the first 3 scheduled doses). |
| Withdrawal from study following hospital discharge | Hypothetical: The time to hospital discharge will be used regardless of study withdrawal where discharge was sustained for 7 days. Otherwise patients will be censored at the last date known to be hospitalised for patients who withdrew during the 7 day rebound period. This approach has been proposed because discontinuation during the rebound period is expected to be due to lack of interest/lack of motivation/lack of time to continue participating in the study rather than relapse. |
| Withdrawal from study prior to hospital discharge | While-on-study: Time to hospital discharge will be right censored at the time of withdrawal from the study or at 28 days, whichever occurs first. The evaluation period for this endpoint is 28 days, therefore estimating the time to hospital |

| | |
|---|---|
| | discharge after Day 28 would not be appropriate. Premature study withdrawal is expected to be independent to the treatment effect, therefore a censoring approach in this scenario is considered appropriate. |
| Other protocol deviations affecting efficacy | Hypothetical (estimand for a situation with no protocol deviations affecting efficacy): To establish the true treatment effect the time to hospital discharge will be considered missing if protocol deviations affecting efficacy are recorded on or prior to Day 35. |
| Medications affecting efficacy | Treatment policy: Time to hospital discharge will be used regardless of any concomitant medication use. |

A second supportive estimand will estimate the hazard ratio of SNG001 versus placebo for the time to hospital discharge of patients in the per protocol population who do not receive medications affecting efficacy. Medications affecting efficacy will be defined as COVID-19 therapies which are approved for use (including emergency use) at the time of the primary analysis and will be handled as per table 10.

**Table 10: Intercurrent events and policies for the second supportive estimand of time to hospital discharge**

| Intercurrent event | Policy |
|---|---|
| Death | Composite variable: Patients who die during the study period will have time to hospital discharge right censored at 28 days (the maximum time to discharge). |
| Missed 2 of the first 3 scheduled doses | Hypothetical (estimand for a situation with treatment compliance): The time to hospital discharge will be considered missing if two or more doses of the randomised treatment were missed within the first three days of therapy, with the corresponding patients excluded from the PP analysis set. A single dose within the first three scheduled dosing days is not expected to be sufficient for the study drug to be effective, therefore this approach will help establish the true treatment effect. It is assumed that such exclusions are not related to treatment. |
| Other premature treatment discontinuation and missed doses | Treatment policy: The time to hospital discharge will be used regardless of treatment discontinuation and the number of missed doses (other than missing 2 out of the first 3 scheduled doses). |
| Withdrawal from study following hospital discharge | Hypothetical: The time to hospital discharge will be used regardless of study withdrawal where discharge was sustained for 7 days. Otherwise patients will be censored at the last date known to be hospitalised for patients who withdrew during the 7 day rebound period. This approach has been proposed because discontinuation during the rebound period is expected to be due to lack of interest/lack of motivation/lack of time to continue participating in the study rather than relapse. |

| | |
|---|---|
| Withdrawal from study prior to hospital discharge | While-on-study: Time to hospital discharge will be right censored at the time of withdrawal from the study or at 28 days, whichever occurs first. The evaluation period for this endpoint is 28 days, therefore estimating the time to hospital discharge after Day 28 would not be appropriate. Premature study withdrawal is expected to be independent to the treatment effect, therefore a censoring approach in this scenario is considered appropriate. |
| Other protocol deviations and prior medications affecting efficacy | Hypothetical (estimand for a situation with no protocol deviations or prior medications affecting efficacy): To establish the true treatment effect the time to hospital discharge will be considered missing if protocol deviations affecting efficacy are recorded on or prior to Day 35 or medications affecting efficacy are being received at the time of first dose. |
| Concomitant medications affecting efficacy | Composite: If approved COVID-19 treatments are given the patients receiving them will be right censored at date prior to first medication use. |

#### *9.1.1.5 Analysis of the Supportive Estimands*

The supportive estimand of the time to hospital discharge primary endpoint will be analysed using the same methods as the primary estimand, as detailed in Section 9.1.1.2.

### 9.1.2 Time to Recovery

#### *9.1.2.1 Primary Estimand*

The second primary estimand will be the hazard ratio of SNG001 versus placebo for the time to recovery of patients in the ITT population. Intercurrent events will be handled as per table 11.

**Table 11: Intercurrent events and policies for the primary estimand of time to recovery**

| Intercurrent event | Policy |
|---|---|
| Death | Composite variable: Patients who die during the study period will have time to recovery right censored at 28 days (the maximum possible time to recovery). |
| Premature treatment discontinuation and missed doses | Treatment policy: The time to recovery will be used regardless of treatment discontinuation and the number of missed doses. |
| Withdrawal from study following recovery | Hypothetical: The time to recovery will be used regardless of study withdrawal where recovery was sustained for 7 days Otherwise patients will be censored at the last date known to have limitation of activities for patients who withdrew during the 7 day rebound period. This approach has been proposed because discontinuation during the rebound period is expected to be due to lack of interest/lack of motivation/lack of time to continue participating in the study rather than relapse. |

| | |
|---|---|
| Withdrawal from study prior to recovery | While-on-study: Time to recovery will be right censored at the time of withdrawal from the study or at 28 days, whichever occurs first. The evaluation period for this endpoint is 28 days, therefore estimating the time to recovery after Day 28 would not be appropriate. Premature study withdrawal is expected to be independent to the treatment effect, therefore a censoring approach in this scenario is considered appropriate. However, this assumption will be tested by appropriate sensitivity analyses. |
| Other protocol deviations and concomitant medications affecting efficacy | Treatment policy: Time to recovery will be used regardless of any concomitant medication use or protocol deviations. |

#### *9.1.2.2 Analysis of the Primary Estimand*

Time to recovery will be analysed using the same methods as time to hospital discharge, as detailed in Section 9.1.1.2.

#### *9.1.2.3 Sensitivity Analyses of the Primary Estimand*

The sensitivity to missing data will be assessed in the same way as described for time to hospital discharge in Section 9.1.1.3.

The primary estimand will be further evaluated for each of the subgroups described in Section 7.2. The analysis method for time to hospital discharge described in Section 9.1.1.2 will be used to evaluate each subgroup.

#### *9.1.2.4 Supportive Estimands*

A supportive estimand of the primary endpoint will estimate the hazard ratio of SNG001 versus placebo for the time to recovery of patients in the per protocol population. Reasons for excluding patients from the PP population are described in Section 7.1.2. Of note, many of the reasons are based on assessments prior to randomisation and treatment and so the exclusions are independent of treatment. Intercurrent events will be handled as per table 12.

**Table 12: Intercurrent events and policies for the supportive estimand of time to recovery**

| Intercurrent event | Policy |
|---|---|
| Death | Treatment policy: Patients who die during the study period will have time to recovery right censored at 28 days (the maximum possible time to recovery). |
| Missed 2 of the first 3 scheduled doses | Hypothetical (estimand for a situation with treatment compliance): The time to recovery will be considered missing if two or more doses of the randomised treatment were missed within the first three days of therapy, with the corresponding patients excluded from the PP analysis set. A single dose within the first three scheduled dosing days is not expected to be sufficient for the study drug to be effective, therefore this approach will help establish the true treatment effect. It is assumed that such exclusions are not related to treatment. |
| Other premature treatment discontinuation and missed doses | Treatment policy: The time to recovery will be used regardless of treatment discontinuation and the number of missed doses (other than missing 2 out of the first 3 scheduled doses). |
| Withdrawal from study following recovery | Hypothetical: The time to recovery will be used regardless of study withdrawal where recovery was sustained for 7 days Otherwise patients will be censored at the last date known to have limitation of activities for patients who withdrew during the 7 day rebound period. This approach has been proposed because discontinuation during the rebound period is expected to be due to lack of interest/lack of motivation/lack of time to continue participating in the study rather than relapse. |
| Withdrawal from study prior to recovery | While-on-study: Time to recovery will be right censored at the time of withdrawal from the study or at 28 days, whichever occurs first. The evaluation period for this endpoint is 28 days, therefore estimating the time to recovery after Day 28 would not be appropriate. Premature study withdrawal is expected to be independent to the treatment effect, therefore a censoring approach in this scenario is considered appropriate. |
| Other protocol deviations affecting efficacy | Hypothetical (estimand for a situation with no deviations affecting efficacy): To establish the true treatment effect the time to recovery will be considered missing if protocol deviations affecting efficacy are recorded on or prior to Day 35. |
| Medications affecting efficacy | Treatment policy: Time to recovery will be used regardless of any concomitant medication use. |

A second supportive estimand will estimate the hazard ratio of SNG001 versus placebo for the time to recovery of patients in the per protocol population who do not receive medications affecting efficacy. Medications affecting efficacy will be defined as COVID-19 therapies which are approved for use (including emergency use) at the time of the primary analysis and will be handled as per table 13.

**Table 13: Intercurrent events and policies for the second supportive estimand of time to recovery**

| Intercurrent event | Policy |
|---|---|
| Death | Treatment policy: Patients who die during the study period will have time to recovery right censored at 28 days (the maximum possible time to recovery). |
| Missed 2 of the first 3 scheduled doses | Hypothetical (estimand for a situation with treatment compliance): The time to recovery will be considered missing if two or more doses of the randomised treatment were missed within the first three days of therapy, with the corresponding patients excluded from the PP analysis set. A single dose within the first three scheduled dosing days is not expected to be sufficient for the study drug to be effective, therefore this approach will help establish the true treatment effect. It is assumed that such exclusions are not related to treatment. |
| Other premature treatment discontinuation and missed doses | Treatment policy: The time to recovery will be used regardless of treatment discontinuation and the number of missed doses (other than missing 2 out of the first 3 scheduled doses). |
| Withdrawal from study following recovery | Hypothetical: The time to recovery will be used regardless of study withdrawal where recovery was sustained for 7 days Otherwise patients will be censored at the last date known to have limitation of activities for patients who withdrew during the 7 day rebound period. This approach has been proposed because discontinuation during the rebound period is expected to be due to lack of interest/lack of motivation/lack of time to continue participating in the study rather than relapse. |
| Withdrawal from study prior to recovery | While-on-study: Time to recovery will be right censored at the time of withdrawal from the study or at 28 days, whichever occurs first. The evaluation period for this endpoint is 28 days, therefore estimating the time to recovery after Day 28 would not be appropriate. Premature study withdrawal is expected to be independent to the treatment effect, therefore a censoring approach in this scenario is considered appropriate. |
| Other protocol deviations and prior medications affecting efficacy | Hypothetical (estimand for a situation with no protocol deviations or prior medications affecting efficacy): To establish the true treatment effect the time to recovery will be considered missing if protocol deviations affecting efficacy are recorded on or prior to Day 35 or medications affecting efficacy are being received at the time of first dose. |
| Concomitant medications affecting efficacy | Composite: If approved COVID-19 treatments are given the patients receiving them will be right censored at date prior to first medication use. |

#### *9.1.2.5 Analysis of the Supportive Estimands*

The supportive estimand of the time to recovery primary endpoint will be analysed using the same methods as the primary estimand for hospital discharge, as detailed in Section 9.1.1.2.

## 9.2 Key Secondary Endpoints

### 9.2.1 Progression to Severe Disease or Death

#### *9.2.1.1 Key Secondary Estimand*

The key secondary estimand will be the difference in probabilities for SNG001 versus placebo for progression to severe disease or death within 35 days of first dose of patients in the ITT population. Intercurrent events will be handled as per Table 14.

**Table 14: Intercurrent events and policies for the key secondary estimand of progression to severe disease or death**

| Intercurrent event | Policy |
|---|---|
| Death | Composite variable: The definition of the endpoint includes patients who die within 35 days of first dose, regardless of their OSCI assessments. |
| Premature treatment discontinuation and missed doses | Treatment policy: Severe disease will be determined regardless of treatment discontinuation and the number of missed doses. |
| Withdrawal from study | While-on-study: Patients will only be considered having severe disease if observed and recorded whilst participating in the study. This assumes the treatment effect is independent to reason for study withdrawal. |
| Other protocol deviations and concomitant medications affecting efficacy | Treatment policy: Severe disease will be determined regardless of any concomitant medication use or protocol deviations. |

#### *9.2.1.2 Analysis of the Key Secondary Estimand*

The key secondary analysis of progression to severe disease or death will be a logistic regression model.

Covariates will be included in the logistic regression model as per Section 7.2.

The number and percentage of patient with severe disease or who died within each treatment group will be presented with the difference in the proportions of patients with severe disease or who died between the treatment groups. The difference in proportions will be calculated using the methods proposed by Ge et al [9]. In addition, the odds ratio, the 95% CI for the odds ratio and the associated p-value will be displayed.

If quasi-complete separation of a covariate occurs the Firth logistic regression method will be used to avoid using maximum likelihood estimation when calculating the estimates.

The Hochberg procedure used in the primary analysis will dictate whether the statistical significance of the key secondary analysis of progression to severe disease or death will be formally assessed, as detailed in Section 7.6 and a statistically significant p-value according to the multiple testing strategy will be indicated in the output.

The odds ratios for severe disease or death, intubation or death and death in SNG001 versus placebo and their corresponding 95% CI and p-values will be presented in a forest plot, in which the x-axis will represent the odds ratios and the y-axis will stand for the estimates of the three key secondary endpoints.

#### *9.2.1.3 Sensitivity Analyses of the Key Secondary Estimand*

The sensitivity of the key secondary analysis to missing data due to withdrawal from study prior to progression to severe disease or death will be assessed firstly through a tipping point analysis for a range of sensitivity parameters, $\delta_i$, for each $i^{th}$ patient. $\delta_i$ represents the change to the odds of severe disease or death. If $\delta_i$ is set to 1 this will represent a Missing at Random (MAR) approach, if $\delta_i < 1$ the imputed OSCI score will be lower than that of the MAR approach and progression to severe disease will be less common. If $\delta_i > 1$ the imputed OSCI score will be higher than that of the MAR approach and progression to severe disease will be more common. Values of $\delta$ will be varied independently for each treatment group.

Missing data will be imputed in M datasets. OSCI will be considered a categorical variable and the imputation algorithm will use a monotone logistic regression method to impute missing OSCI scores. Each of the covariates used in the primary analysis, including treatment group, will be included as covariates in the logistic regression. Missing data will be imputed iteratively by day, starting at day 2. For each subsequent day, the OSCI scores at prior days will be included as covariates, including the OSCI scores imputed in earlier iterations. This will not include the OSCI score at day 1 because this will always be 4, by design. However, because there are 34 scheduled visit days to be imputed in this way it is likely as the imputation progresses that the imputation model will become over-parameterised. To avoid this issue and to account for the fact that the most recent days are most likely to be predictive, only the OSCI score at the previous two days will be used as continuous covariates. Any imputations of 8 (death) will be “carried forward” to all future missing days after each step and not imputed again.

For each imputed dataset and for each value of $\delta_i$ the primary analysis method will be repeated. The estimates from the imputed datasets will be combined for each value of $\delta_i$ using Rubin’s rules. The results for the different combinations of $\delta_i$ for Placebo and SNG001 patients will be plotted on a heat map to identify, if applicable, where the p-values becomes insignificant. This ‘tipping point’ will also be tabulated along with specific values of $\delta_i$.

A second sensitivity of the primary analysis to missing data will follow the jump to reference MNAR method of imputation detailed in Section 9.1.1.3. The key secondary analysis model will be repeated for each imputed dataset and the combined estimates, as calculated by Rubin’s rules will be tabulated.

The above sensitivity analyses represent a change to the handling of the intercurrent event 'Withdrawal from study' to a treatment policy.

A third sensitivity analysis will be performed on the subset of patients who have completed Day 35 or who have died prior to Day 35. Patients who did not withdraw prior to Day 35 and who have at least 1 completed assessment between Day 31 and Day 35 will be considered completers. This is to exclude patients who are lost to follow-up during the first 35 days of the study but are re-contacted at a later date. The key secondary analysis model will be repeated for this subset.

#### *9.2.1.3.1 Sensitivity to the Severe Disease Definition*

The following analyses will explore different subsets of the progressed population:

- A sensitivity analysis which will only consider OSCI assessments between Day 6 and Day 35 for the derivation of progression to severe disease or death. The purpose of this analysis is to assess the rate of progression after a sufficient period of time has passed for the study drug to have a beneficial effect. Patients who die prior to Day 6 will be excluded from the analysis.
- A sensitivity analysis which will exclude short term progressions. Short term progressions are defined by OSCI scores of ≥5 which are not maintained for consecutive scheduled assessments.
- A summary of patients with a maximum OSCI score of 5. This summary will assess patients who progress to non-invasive or high flow oxygen but who do not progress to intubation.
- A summary of patients who progress to severe disease but are subsequently discharged from hospital.
- A summary of patients who progress to severe disease but subsequently recover.

#### *9.2.1.4 Supportive Estimands*

A supportive estimand for the key secondary endpoint will be defined as follows. The difference in probabilities for SNG001 versus placebo for progression to severe disease or death within 35 days of first dose will be estimated for the per protocol population. Reasons for excluding patients from the PP population are described in Section 7.1.2. Of note, many of the reasons are based on assessments prior to randomisation and treatment and so the exclusions are independent of treatment. Intercurrent events will be handled as per table 15.

**Table 15: Intercurrent events and policies for the supportive estimand of progression to severe disease or death**

| Intercurrent event | Policy |
|---|---|
| Death | Composite variable: The definition of severe disease includes patients who die within 35 days of first dose, regardless of their OSCI assessments. |
| Missed 2 of the first 3 scheduled doses | Hypothetical (estimand for a situation with treatment compliance): OSCI assessments will be considered missing if two doses or more of the randomised treatment were missed within the first three days of therapy, with the corresponding patients excluded from the PP analysis set. A single dose within the first three scheduled dosing days is not expected to be sufficient for the study drug to be effective, therefore this |

| | |
|---|---|
| | approach will help establish the true treatment effect. It is assumed that such exclusions are not related to treatment. |
| Other premature treatment discontinuation and missed doses | Treatment policy: Severe disease will be determined regardless of treatment discontinuation and the number of missed doses (other than missing 2 out of the first 3 scheduled doses). |
| Withdrawal from study | While-on-study: Patients will only be considered having severe disease if observed and recorded whilst participating in the study. This assumes the treatment effect is independent to reason for study withdrawal. |
| Other protocol deviations affecting efficacy | Hypothetical (estimand for a situation with no protocol deviations affecting efficacy): To establish the true treatment effect all OSCI assessments will be considered missing if protocol deviations affecting efficacy are recorded on or prior to Day 35. |
| Medications affecting efficacy | Treatment policy: Severe disease will be determined regardless of any concomitant medication use. |

A second supportive estimand will estimate the difference in probabilities for SNG001 versus placebo for progression to severe disease or death within 35 days of first dose in the per protocol population who do not receive medications affecting efficacy. Medications affecting efficacy will be defined as COVID-19 therapies which are approved for use (including emergency use) at the time of the primary analysis and will be handled as per table 16.

**Table 16: Intercurrent events and policies for the second supportive estimand of progression to severe disease or death**

| Intercurrent event | Policy |
|---|---|
| Death | Composite variable: The definition of severe disease includes patients who die within 35 days of first dose, regardless of their OSCI assessments. |
| Missed 2 of the first 3 scheduled doses | Hypothetical (estimand for a situation with treatment compliance): OSCI assessments will be considered missing if two doses or more of the randomised treatment were missed within the first three days of therapy, with the corresponding patients excluded from the PP analysis set. A single dose within the first three scheduled dosing days is not expected to be sufficient for the study drug to be effective, therefore this approach will help establish the true treatment effect. It is assumed that such exclusions are not related to treatment. |
| Other premature treatment discontinuation and missed doses | Treatment policy: Severe disease will be determined regardless of treatment discontinuation and the number of missed doses (other than missing 2 out of the first 3 scheduled doses). |

| | |
|---|---|
| Withdrawal from study | While-on-study: Patients will only be considered having severe disease if observed and recorded whilst participating in the study. This assumes the treatment effect is independent to reason for study withdrawal. |
| Other protocol deviations and prior medications affecting efficacy | Hypothetical (estimand for a situation with no protocol deviations or prior medications affecting efficacy): To establish the true treatment effect all OSCI assessments will be considered missing if protocol deviations affecting efficacy are recorded on or prior to Day 35 or medications affecting efficacy are being received at the time of first dose. |
| Concomitant medications affecting efficacy | Composite: Only assessments prior to the first dose of any medication affecting efficacy will be considered for the derivation of severe disease. |

#### *9.2.1.5 Analysis of the Supportive Estimands*

The supportive estimand of progression to severe disease or death will be analysed using the same methods as the key secondary estimand, as detailed in Section 9.2.1.2.

### 9.2.2 Progression to Intubation or Death

#### *9.2.2.1 Key Secondary Estimand*

The key secondary estimand will be the difference in probabilities for SNG001 versus placebo for progression to intubation or death within 35 days of first dose of patients in the ITT population. Intercurrent events will be handled as per Table 17.

**Table 17: Intercurrent events and policies for the key secondary estimand of progression to intubation or death**

| Intercurrent event | Policy |
|---|---|
| Death | Composite variable: The definition of the endpoint includes patients who die within 35 days of first dose, regardless of their OSCI assessments. |
| Premature treatment discontinuation and missed doses | Treatment policy: Intubation or death will be determined regardless of treatment discontinuation and the number of missed doses. |
| Withdrawal from study | While-on-study: Patients will only be considered to be intubated if observed and recorded whilst participating in the study. This assumes the treatment effect is independent to reason for study withdrawal. |
| Other protocol deviations and concomitant medications affecting efficacy | Treatment policy: Intubation or death will be determined regardless of any concomitant medication use or protocol deviations. |

#### *9.2.2.2 Analysis of the Key Secondary Estimand*

Progression to intubation or death will be analysed using the same methods as progression to severe disease or death, as detailed in Section 9.2.1.2.

#### *9.2.2.3 Sensitivity Analyses of the Key Secondary Estimand*

The sensitivity to missing data will be assessed in the same way as described for progression to severe disease or death in Section 9.2.1.3.

##### *9.2.2.3.1 Sensitivity to the Severe Disease Definition*

The following analyses will explore different subsets of the progressed population:

- A sensitivity analysis which will only consider OSCI assessments between Day 6 and Day 35 for the derivation of progression to intubation or death. The purpose of this analysis is to assess the rate of progression after a sufficient period of time has passed for the study drug to have a beneficial effect. Patients who die prior to Day 6 will be excluded from the analysis.
- A sensitivity analysis which will exclude short term progressions. Short term progressions are defined by OSCI scores of ≥6 which are not maintained for consecutive scheduled assessments.
- A summary of patients with a maximum OSCI score of 6. This summary will assess patients who progress to intubation but who do not progress to additional organ support.
- A summary of patients who progress to intubation but are subsequently discharged from hospital.
- A summary of patients who progress to intubation but subsequently recover.

#### *9.2.2.4 Supportive Estimands*

A supportive estimand for the key secondary endpoint will be defined as follows. The difference in probabilities for SNG001 versus placebo for progression to intubation or death within 35 days of first dose will be estimated for the per protocol population. Reasons for excluding patients from the PP population are described in Section 7.1.2. Of note, many of the reasons are based on assessments prior to randomisation and treatment and so the exclusions are independent of treatment. Intercurrent events will be handled as per table 18.

**Table 18: Intercurrent events and policies for the supportive estimand of progression to intubation or death**

| Intercurrent event | Policy |
|---|---|
| Death | Composite variable: The definition of the endpoint includes patients who die within 35 days of first dose, regardless of their OSCI assessments. |
| Missed 2 of the first 3 scheduled doses | Hypothetical (estimand for a situation with treatment compliance): OSCI assessments will be considered missing if two doses or more of the randomised treatment were missed within the first three days of therapy, with the corresponding patients excluded from the PP analysis set. A single dose within the first three scheduled dosing days is not expected to be sufficient for the study drug to be effective, therefore this |

| | |
|---|---|
| | approach will help establish the true treatment effect. It is assumed that such exclusions are not related to treatment. |
| Other premature treatment discontinuation and missed doses | Treatment policy: Intubation will be determined regardless of treatment discontinuation and the number of missed doses (other than missing 2 out of the first 3 scheduled doses). |
| Withdrawal from study | While-on-study: Patients will only be considered as intubated if observed and recorded whilst participating in the study. This assumes the treatment effect is independent to reason for study withdrawal. |
| Other protocol deviationsaffecting efficacy | Hypothetical (estimand for a situation with no protocol deviations affecting efficacy): To establish the true treatment effect all OSCI assessments will be considered missing if protocol deviations affecting efficacy are recorded on or prior to Day 35. |
| Medications affecting efficacy | Treatment policy: Intubation will be determined regardless of any concomitant medication use. |

A second supportive estimand will estimate the difference in probabilities for SNG001 versus placebo for progression to intubation or death within 35 days of first dose in the per protocol population who do not receive medications affecting efficacy. Medications affecting efficacy will be defined as COVID-19 therapies which are approved for use (including emergency use) at the time of the primary analysis and will be handled as per table 19.

**Table 19: Intercurrent events and policies for the second supportive estimand of progression to intubation or death**

| Intercurrent event | Policy |
|---|---|
| Death | Composite variable: The definition of the endpoint includes patients who die within 35 days of first dose, regardless of their OSCI assessments. |
| Missed 2 of the first 3 scheduled doses | Hypothetical (estimand for a situation with treatment compliance): OSCI assessments will be considered missing if two doses or more of the randomised treatment were missed within the first three days of therapy, with the corresponding patients excluded from the PP analysis set. A single dose within the first three scheduled dosing days is not expected to be sufficient for the study drug to be effective, therefore this approach will help establish the true treatment effect. It is assumed that such exclusions are not related to treatment. |

| | |
|---|---|
| Other premature treatment discontinuation and missed doses | Treatment policy: Intubation will be determined regardless of treatment discontinuation and the number of missed doses (other than missing 2 out of the first 3 scheduled doses). |
| Withdrawal from study | While-on-study: Patients will only be considered as intubated if observed and recorded whilst participating in the study. This assumes the treatment effect is independent to reason for study withdrawal. |
| Other protocol deviations and prior medications affecting efficacy | Hypothetical (estimand for a situation with no protocol deviations or prior medications affecting efficacy): To establish the true treatment effect all OSCI assessments will be considered missing if protocol deviations affecting efficacy are recorded on or prior to Day 35 or medications affecting efficacy are being received at the time of first dose. |
| Concomitant medications affecting efficacy | Composite: Only assessments prior to the first dose of any medication affecting efficacy will be considered for the derivation of intubation. |

#### *9.2.2.5 Analysis of the Supportive Estimands*

The supportive estimand of progression to intubation or death will be analysed using the same methods as progression to severe disease or death, as detailed in Section 9.2.1.2.

### 9.2.3 Death

#### *9.2.3.1 Key Secondary Estimand*

The key secondary estimand will be the difference in probabilities for SNG001 versus placebo for death within 35 days of first dose of patients in the ITT population. Intercurrent events will be handled as per Table 20.

**Table 20: Intercurrent events and policies for the key secondary estimand of death**

| Intercurrent event | Policy |
|---|---|
| Premature treatment discontinuation and missed doses | Treatment policy: Death will be determined regardless of treatment discontinuation and the number of missed doses. |
| Withdrawal from study | While-on-study: Deaths which occur after study withdrawal will not be considered, unless consent is received to include death details in the clinical study database. This assumes the treatment effect is independent to reason for study withdrawal. |
| Other protocol deviations and concomitant medications affecting efficacy | Treatment policy: Death will be determined regardless of any concomitant medication use or protocol deviations. |

#### *9.2.3.2 Analysis of the Key Secondary Estimand*

Death will be analysed using the same methods as progression to severe disease or death, as detailed in Section 9.2.1.2.

#### *9.2.3.3 Sensitivity Analyses of the Key Secondary Estimand*

The sensitivity to missing data will be assessed in the same way as described for progression to severe disease or death in Section 9.2.1.3.

##### *9.2.3.3.1 Sensitivity to the Severe Disease Definition*

The following analyses will explore different subsets of the progressed population:

- A sensitivity analysis which will only consider OSCI assessments between Day 6 and Day 35 for the derivation of death. The purpose of this analysis is to assess the rate of mortality after a sufficient period of time has passed for the study drug to have a beneficial effect.

#### *9.2.3.4 Supportive Estimands*

A supportive estimand for the key secondary endpoint will be defined as follows. The difference in proportions for SNG001 versus placebo for death within 35 days of first dose will be estimated for the per protocol population. Reasons for excluding patients from the PP population are described in Section 7.1.2. Of note, many of the reasons are based on assessments prior to randomisation and treatment and so the exclusions are independent of treatment. Intercurrent events will be handled as per table 21.

**Table 21: Intercurrent events and policies for the supportive estimand of death**

| Intercurrent event | Policy |
|---|---|
| Missed 2 of the first 3 scheduled doses | Hypothetical (estimand for a situation with treatment compliance): OSCI assessments will be considered missing if two doses or more of the randomised treatment were missed within the first three days of therapy, with the corresponding patients excluded from the PP analysis set. A single dose within the first three scheduled dosing days is not expected to be sufficient for the study drug to be effective, therefore this approach will help establish the true treatment effect. It is assumed that such exclusions are not related to treatment. |
| Other premature treatment discontinuation and missed doses | Treatment policy: Death will be determined regardless of treatment discontinuation and the number of missed doses (other than missing 2 out of the first 3 scheduled doses). |
| Withdrawal from study | While-on-study: Patients will only be considered as intubated if observed and recorded whilst participating in the study. This assumes the treatment effect is independent to reason for study withdrawal. |
| Other protocol deviations affecting efficacy | Hypothetical (estimand for a situation with no protocol deviations affecting efficacy): To establish the true treatment effect all OSCI assessments will be considered missing if protocol deviations affecting efficacy are recorded on or prior to Day 35. |

| | |
|---|---|
| Medications affecting efficacy | Treatment policy: Death will be determined regardless of any concomitant medication use. |

A second supportive estimand will estimate the difference in probabilities for SNG001 versus placebo for death within 35 days of first dose in the per protocol population who do not receive medications affecting efficacy. Medications affecting efficacy will be defined as COVID-19 therapies which are approved for use (including emergency use) at the time of the primary analysis and will be handled as per table 22.

**Table 22: Intercurrent events and policies for the second supportive estimand of death**

| Intercurrent event | Policy |
|---|---|
| Missed 2 of the first 3 scheduled doses | Hypothetical (estimand for a situation with treatment compliance): OSCI assessments will be considered missing if two doses or more of the randomised treatment were missed within the first three days of therapy, with the corresponding patients excluded from the PP analysis set. A single dose within the first three scheduled dosing days is not expected to be sufficient for the study drug to be effective, therefore this approach will help establish the true treatment effect. It is assumed that such exclusions are not related to treatment. |
| Other premature treatment discontinuation and missed doses | Treatment policy: Death will be determined regardless of treatment discontinuation and the number of missed doses (other than missing 2 out of the first 3 scheduled doses). |
| Withdrawal from study | While-on-study: Patients will only be considered as intubated if observed and recorded whilst participating in the study. This assumes the treatment effect is independent to reason for study withdrawal. |
| Other protocol deviations and prior medications affecting efficacy | Hypothetical (estimand for a situation with no protocol deviations or prior medications affecting efficacy): To establish the true treatment effect all OSCI assessments will be considered missing if protocol deviations affecting efficacy are recorded on or prior to Day 35 or medications affecting efficacy are being received at the time of first dose. |
| Concomitant medications affecting efficacy | Composite: Only assessments prior to the first dose of any medication affecting efficacy will be considered for the derivation of death. |

#### *9.2.3.5 Analysis of the Supportive Estimands*

The supportive estimand of death will be analysed using the same methods as progression to severe disease or death, as detailed in Section 9.2.1.2.

## 9.3 Secondary Efficacy Endpoints

### 9.3.1 Secondary Estimands

The estimands for the secondary endpoints are defined in table 23.

**Table 23: Secondary estimand definitions**

| Endpoint | Population of interest | Consideration of intercurrent events | Summary measure |
|---|---|---|---|
| Proportion of recovered patients at days 7, 14, 21 and 28 | ITT | Composite variable: Subjects who die cannot recover, death after recovery will be considered as a rebound.<br>Treatment policy: Regardless of protocol deviations, treatment adherence and any concomitant therapies received for the treatment of SARS-CoV-2.<br>While on study: Recovery will be determined at study withdrawal, if withdrawal occurs prior to day 35. | Difference in proportions for each SNG001 arm versus placebo at each day |
| | Per Protocol | Hypothetical: Estimand for a situation with treatment compliance and no protocol deviations affecting efficacy. | |
| Proportion of patients discharged from hospital at days 7, 14, 21 and 28 | ITT | Composite variable: Subjects who die cannot be discharged, death after discharge will be considered as a rebound.<br>Treatment policy: Regardless of protocol deviations, treatment adherence and any concomitant therapies received for the treatment of SARS-CoV-2.<br>While on study: Discharge will be determined at study withdrawal, if withdrawal occurs prior to day 35. | Difference in proportions for each SNG001 arm versus placebo at each day |
| | Per Protocol | Hypothetical: Estimand for a situation with treatment compliance and no protocol deviations or prior medications affecting efficacy. | |
| Improvement across the entire OSCI scale at days 7, 14, 21 and 28 | ITT | Composite variable: Death is defined by an OSCI score of 8.<br>Treatment policy: Regardless of protocol deviations, treatment adherence and any concomitant therapies received for the treatment of SARS-CoV-2.<br>While on study: OSCI scores following study withdrawal will be considered missing. | Odds ratio for each SNG001 arm versus placebo at each day |
| | Per Protocol | Hypothetical: Estimand for a situation with treatment compliance and no protocol deviations affecting efficacy. | |
| Change in total BCSS score over the study period | ITT | Treatment policy: Regardless of protocol deviations, treatment adherence and any concomitant therapies received for the treatment of SARS-CoV-2. | Difference in LS means between each SNG001 arm versus placebo |

| | | | |
|---|---|---|---|
| | | | averaged over the whole study period |
| Change in breathlessness score over the study period | ITT | Treatment policy: Regardless of protocol deviations, treatment adherence and any concomitant therapies received for the treatment of SARS-CoV-2. | Difference in LS means between each SNG001 arm versus placebo averaged over the whole study period |
| | Per Protocol | Hypothetical: Estimand for a situation with treatment compliance and no protocol deviations affecting efficacy. | |
| Change in cough score over the study period | ITT | Treatment policy: Regardless of protocol deviations, treatment adherence and any concomitant therapies received for the treatment of SARS-CoV-2. | Difference in LS means between each SNG001 arm versus placebo averaged over the whole study period |
| | Per Protocol | Hypothetical: Estimand for a situation with treatment compliance and no protocol deviations affecting efficacy. | |

### 9.3.2 Analysis of Secondary Estimands

#### *9.3.2.1 Recovery at days 7, 14, 21 and 28*

Logistic regression models will be applied to OSCI recovery by days 7, 14, 21 and 28. For recovery by visit a patient will be considered recovered at every visit following the first confirmed recovery. E.g. a patient who recovers at Day 6 will be considered recovered at Days 7, 14, 21 and 28 regardless of what happens after the confirmed recovery.

Covariates will be included in the logistic regression model as per Section 7.2.

The number and percentage of patient who recovered within each treatment group will be presented with the difference in the proportions of patients who recovered between the treatment groups alongside the odds ratios, 95% CI of the odds ratios and p-value from the logistic regression.

If quasi-complete separation of a covariate occurs at any visit the Firth logistic regression method will be used across all visits to avoid using maximum likelihood estimation when calculating the estimates.

The odds ratios for recovery, hospital discharge and improvement across the entire OSCI scale by days 7, 14, 21 and 28 in SNG001 versus placebo and their corresponding 95% CI and p-values will be presented in a forest plot, in which the x-axis will represent the odds ratios and the y-axis will stand for the estimates of the above mentioned secondary endpoints.

The same analysis methods will be used to use to assess both of the estimands in Section 9.3.1.

#### *9.3.2.2 Hospital discharge at days 7, 14, 21 and 28*

Hospital discharge by days 7, 14, 21 and 28 will be assessed using the same methods as recovery at days 7, 14, 21 and 28, as described in Section 9.3.2.1.

#### *9.3.2.3 Improvement across the entire OSCI scale at days 7, 14, 21 and 28*

Improvement across the entire OSCI scale at days 7, 14, 21 and 28 will be analysed through an ordered logistic regression model, assuming proportional odds across the treatment groups.

Covariates will be included in the logistic regression model as per Section 7.2.

The odds ratios will be presented for each visit alongside their 95% CIs and p-values.

If quasi-complete separation occurs due to low incidence of some OSCI levels then neighbouring OSCI levels may be pooled for the purpose of the analysis to a minimum of two levels (≤3 and ≥4), in which case the analysis will simplify to a binary logistic regression. Also, covariates may be dropped from the analysis if it is clear that the cause of quasi-complete separation is a particular categorised covariate.

The proportional odds assumption will be tested by re-running the ordered logistic regression model with both unequal and equal slopes for the treatment effect and equal slopes for all other covariates. Proportionality will be assessed by the statistical significance of the treatment effect for unequal slopes, at the 5% significance level.

The same analysis methods will be used to use to assess both of the estimands in Section 9.3.1.

A sensitivity analysis of the estimand using the ITT population will be performed where OSCI levels of 0 and 1 will be derived based on the COVID-19 symptom assessments. An OSCI score of 0 will be assigned if no COVID-19 symptoms are present, regardless of the OSCI score recorded in the clinical database. An OSCI score of 1 will be assigned if any COVID-19 symptoms are present and an OSCI score of 0 was recorded in the clinical trial database. The number and percentage of patients with a rederived OSCI score will be presented at each time point along with the odds ratios and their 95% CIs and p-values.

The number and percentage of patients with each OSCI score at each post baseline visit will also be presented.

#### *9.3.2.4 Change in total BCSS score*

Change in total BCSS score over the treatment period will be assessed by an MMRM.

Covariates will be included in the MMRM as per Section 7.2, plus covariates for baseline total BCSS score, scheduled visit, an interaction term for treatment by visit and an interaction term for baseline total BCSS score by visit.

Also, estimates of the mean change (± 95% CI) in total BCSS score as well as the estimated mean change (± SE) in the individual BCSS scales over the treatment period as calculated by the MMRM analysis will be presented for SNG001 versus placebo in a panel plot.

Data from the follow-up visits or early withdrawal visits after day 15 will not be included in the analysis. The model will be fit for absolute score and change from baseline in score: the baseline BCSS covariate ensures that these models have identical treatment effects. Least Squares (LS) means for absolute scores and change from baseline scores and the LS mean difference between treatment groups will be presented for each post baseline visit up to day 15 and across the entire post baseline treatment period (day 2 – 15) with 95% CIs and p-values.

A covariance matrix will be used to account for the within patient correlation. If an unstructured matrix can be used this will be the first choice, otherwise a compound symmetry structure will be used. The

observed margin option will be used to ensure the model coefficients are weighted to reflect the actual proportions of each class level within the data.

Missing data will be handled as per Section 7.3.2.

Absolute values and the change from baseline in total BCSS score will also be summarised over the entire study period.

#### *9.3.2.5 Change in breathlessness and cough scores*

Change in breathlessness and cough scores over the treatment period will be analysed using the same methods described for total BCSS score in Section 9.3.2.4.

Absolute values and the change from baseline in breathlessness, cough and sputum score will be summarised over the entire study period. The change from baseline in each symptom score will also be summarised in shift tables.

### 9.3.3 NEWS2 Score

The absolute NEWS2 scores and the change from baseline in NEWS2 score will be summarised for hospitalised patients at each scheduled assessment. Generally, NEWS2 score will only be calculated from the data recorded in the NEWS2 CRF. However, baseline NEWS2 score will be the calculated from the data entered in the vital signs and level of confusion CRFs for the last assessment prior to first dose. NEWS2 scores will be calculated and summarised from data collected in the NEWS2 CRF for the Pre-dose and Day 1 assessments, however the change from baseline will not be summarised because as per the protocol these assessments could be pre or post dose.

### 9.3.4 Quality of Life

Quality of life as measured by the EQ-5D-5L will be summarised by descriptive statistics of the crosswalk index value, the LSS, the Visual Analogue Scale (VAS) and the usual activities dimension at each scheduled visit.

### 9.3.5 General Anxiety

GAD-7 total scores will be summarised by descriptive statistics and the number and percentage of patients within each anxiety severity category will be displayed at each scheduled assessment.

### 9.3.6 Depression

PHQ-9 total scores will be summarised by descriptive statistics and the number and percentage of patients within each depression severity category will be displayed at each scheduled assessment.

### 9.3.7 Fatigue

FACIT-FS total scores will be summarised by descriptive statistics at each scheduled assessment.

### 9.3.8 Pain

Descriptive statistics will be presented at each post baseline visit for each pain severity score category, the overall pain severity score and the pain interference score.

### 9.3.9 COVID-19 Symptom Assessments

The number and percentage of patients with any symptom, each individual symptom and any other symptoms associated with COVID-19 will be presented both overall and at each scheduled time point.

## 10 Safety Analyses

All outputs for safety outcomes will use the Safety analysis population.

### 10.1 Adverse Events

Adverse events will be recorded from the time informed consent is given 28 days after the last administration of the study medication. All AEs will be coded using the latest available version of the MedDRA and will be categorized by intensity (mild/moderate/severe) and relationship (unrelated/unlikely to be related/possibly related/probably related/definitely related).

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the administration of study drug or any unresolved event already present before administration of study drug that worsens in intensity following exposure to the treatment. Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent unless they clearly started prior to treatment (as indicated by the month/year if the day is missing etc.).

Summary tables will contain the cumulative incidence rate and the number of events where applicable. A subject who has multiple events in the same SOC and PT will be counted only once in the subject counts but all events will be included. Adverse event summaries will be ordered by the international SOC order (Appendix III) and decreasing frequency of PT within SOC, in the active arm overall column.

Summaries of TEAEs by SOC and PT will include the following:

- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of serious related TEAEs
- Incidence of TEAEs by relationship
- Incidence of TEAEs by severity
- Incidence of TEAEs leading to discontinuation
- Incidence of TEAEs leading to death
- Incidence of related TEAEs leading to death.
- Incidence of TEAEs of special interest.
-

An adverse event summary will summarise the number of TEAEs in each of the above categories alongside 95% Newcombe confidence intervals for the differences in proportions between treatment arms.

Summaries of TEAEs by PT will include the following:

- Incidence of TEAEs
- Incidence of serious TEAEs

- Common TEAEs (occurring in at least 5% of the total study population).

The summary of common TEAE will include 95% Newcombe confidence intervals for the differences in proportions between treatment arms.

In summaries including relationship to study treatment, the following relationships will be considered related: 'Definitely related', 'Probably Related', 'Possibly Related'. 'Unlikely to be Related' and 'Not related' will be considered unrelated.

In summaries including intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Subjects will be counted once under each severity category if the same event was observed at different severities.

An adverse event of special interest (AESI) is an AE that meets the following criteria:

- Moderate or worse palpitations during the dosing period and up to 24 hours after last dose.
- Severe bronchospasm with 4 hours of investigational agent/placebo administration (symptoms causing inability to perform usual social and functional activities and deemed related to the study product as determined by the site investigator).

Adverse events which are coded to more than one preferred term will be counted once under each term.

A listing of serious AEs will also be produced.

### 10.2 Vital Signs

Systolic blood pressure, diastolic blood pressure, heart rate, body temperature, respiratory rate and oxygen saturation absolute and change from baseline values will be summarised by descriptive statistics for each study day. The number and percentage of patients receiving oxygen at each assessment will also be presented. Vital signs will not be collected following discharge from hospital.

### 10.3 Level of Consciousness or new Confusion

Level of consciousness or new confusion will be summarised by shift tables from baseline to each post baseline timepoint. Data will be collected whilst patients are hospitalised only.

### 10.4 Physical Examination

Physical examination findings will be listed only.

## 11 Immunogenicity

The number and percentage of patients with anti-drug antibodies at day 44 will be presented. In addition, the number and percentage of patients with anti-drug antibodies at day 44 who did not have anti-drug antibodies at screening will also be presented. Antibody titres will be listed, if available.

## 12 CCI

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[redacted]

## 13 Reporting Conventions

When reporting relative frequencies or other percentage values, the following rules apply:

- For values where all subjects fulfil certain criteria, the percentage value will be displayed as 100.
- For values where the absolute frequency is 0, there will be no percentage presented at all.
- All other percentage displays will use 1 decimal place.

When reporting descriptive statistics, the following rules will apply in general:

- n will be an integer
- Mean (arithmetic and geometric), and median will use 1 decimal place more than the original data.
- Coefficient of variation and geometric CV will be reported as a percentage to 1 decimal place.
- SD will use 2 decimal places more than the original data.
- Minimum and maximum will be reported using the same number of decimal places as the original value.
- If no subjects have data at a given timepoint then only n=0 will be presented. However, if n < 3, present the n, min and maximum only. If n = 3, n, mean, median, minimum and maximum will be presented only. The other descriptive statistics will be left blank.
- P-values ≥ 0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as “<0.001”; p-values greater than 0.999 will be reported as “>0.999”.

- Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

## 14 Technical Details

Statistical evaluation will be performed by CCI CCI and supervised by Synairgen unless otherwise indicated.

The datasets will follow Clinical Data Interchange Standards Consortium (CDISC) standards.

All analyses will be performed using CCI (CCI) or CCI or higher.

## 15 Summary of Changes to the Protocol

The protocol defines hospital discharge as an OSCI ≤ 2 without rebound and similarly recovery is defined as an OSCI ≤ 1 without rebound. However, the protocol does not give a time period for assessing rebound. If all subsequent assessments are included to assess rebound this creates a bias because earlier hospital discharge/recovery times require a longer period of sustainability. Also, patients who withdraw from the study immediately after hospital/discharge recovery cannot be assessed for rebound.

To address this issue a fixed rebound period of 7 days has been defined for assessing hospital discharge and recovery, which will be applied regardless of when hospital discharge or recovery happens and regardless of study withdrawal.

In addition, the protocol defines a list of covariates to be included in each analysis, however to simplify the planned analyses these have been reduced to a smaller set of covariates which are considered the best predictors for COVID-19 progression and recovery.

In addition, the estimands based on the per protocol population have been modified with regards to medications affecting efficacy (approved COVID-19 therapies) because it has been recognised that use of such therapies is not a protocol deviation. Therefore, a second supportive estimand has been included which accounts for intercurrent events related to medications affecting efficacy. Although such medications are allowed by the protocol it is thought that initiating such therapies during the study may reflect a prior lack of efficacy and starting such therapies prior to the study may impact the true effect of the study treatment.

## 16 References

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[10] Feng, YS., Jiang, R., Pickard, A.S. et al. Combining EQ-5D-5L items into a level summary score: demonstrating feasibility using non-parametric item response theory using an international dataset. Qual Life Res (2021). https://doi.org/10.1007/s11136-021-02922-1

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## 17 Appendices

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### 17.3 APPENDIX III – MedDRA Internationally Agreed Order for System Organ Class

| Order Number | System Organ Class |
|---|---|
| 1 | Infections and infestations |
| 2 | Neoplasms benign, malignant and unspecified (incl cysts and polyps) |
| 3 | Blood and lymphatic system disorders |
| 4 | Immune system disorders |
| 5 | Endocrine disorders |
| 6 | Metabolism and nutrition disorders |
| 7 | Psychiatric disorders |
| 8 | Nervous system disorders |
| 9 | Eye disorders |
| 10 | Ear and labyrinth disorders |
| 11 | Cardiac disorders |
| 12 | Vascular disorders |
| 13 | Respiratory, thoracic and mediastinal disorders |
| 14 | Gastrointestinal disorders |
| 15 | Hepatobiliary disorders |
| 16 | Skin and subcutaneous tissue disorders |
| 17 | Musculoskeletal and connective tissue disorders |
| 18 | Renal and urinary disorders |
| 19 | Pregnancy, puerperium and perinatal conditions |
| 20 | Reproductive system and breast disorders |
| 21 | Congenital, familial and genetic disorders |
| 22 | General disorders and administration site conditions |
| 23 | Investigations |
| 24 | Injury, poisoning and procedural complications |
| 25 | Surgical and medical procedures |
| 26 | Social circumstances |
| 27 | Product issues |

DocuSign

## Certificate Of Completion

Envelope Id: PPD
Status: Completed
Subject: Please DocuSign: SG018_SAP_Final_RotW v1.0 08FEB2022_clean.docx
Source Envelope:
Document Pages: 58
Signatures: 4
Envelope Originator:
Certificate Pages: 5
Initials: 0
PPD
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: PPD

## Record Tracking

Status: Original
Holder:
Location: DocuSign
PPD
PPD

| Signer Events | Signature | Timestamp |
|---|---|---|
| PPD<br>PPD<br>PPD<br>Security Level: Email, Account Authentication (Required) | DocuSigned by:<br>PPD | PPD<br>PPD<br>PPD |

With Signing Authentication via DocuSign password
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PPD

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Security Level: Email, Account Authentication (Required)

PPD

With Signing Authentication via DocuSign password
With Signing Reasons (on each tab):
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**Electronic Record and Signature Disclosure:**
PPD

| Signer Events | | Timestamp |
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| PPD<br>PPD<br>PPD<br>Security Level: Email, Account Authentication (Required), Logged in | PPD<br>With Signing Authentication via DocuSign password<br>With Signing Reasons (on each tab):<br>I approve this document | |

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| PPD<br>PPD<br>Synairgen Research Ltd<br>Security Level: Email, Account Authentication (Required) | PPD<br>With Signing Authentication via DocuSign password<br>With Signing Reasons (on each tab):<br>I approve this document | |

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| In Person Signer Events | Signature | Timestamp |
|---|---|---|

| Editor Delivery Events | Status | Timestamp |
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| Agent Delivery Events | Status | Timestamp |
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| Intermediary Delivery Events | Status | Timestamp |
|---|---|---|

| Certified Delivery Events | Status | Timestamp |
|---|---|---|

| Carbon Copy Events | Status | Timestamp |
|---|---|---|

| Witness Events | Signature | Timestamp |
|---|---|---|

| Notary Events | Signature | Timestamp |
|---|---|---|

| Envelope Summary Events | Status | Timestamps |
|---|---|---|
| Envelope Sent | Hashed/Encrypted | PPD |
| Certified Delivered | Security Checked | PPD |
| Signing Complete | Security Checked | PPD |
| Completed | Security Checked | PPD |

| Payment Events | Status | Timestamps |
|---|---|---|

| Electronic Record and Signature Disclosure |
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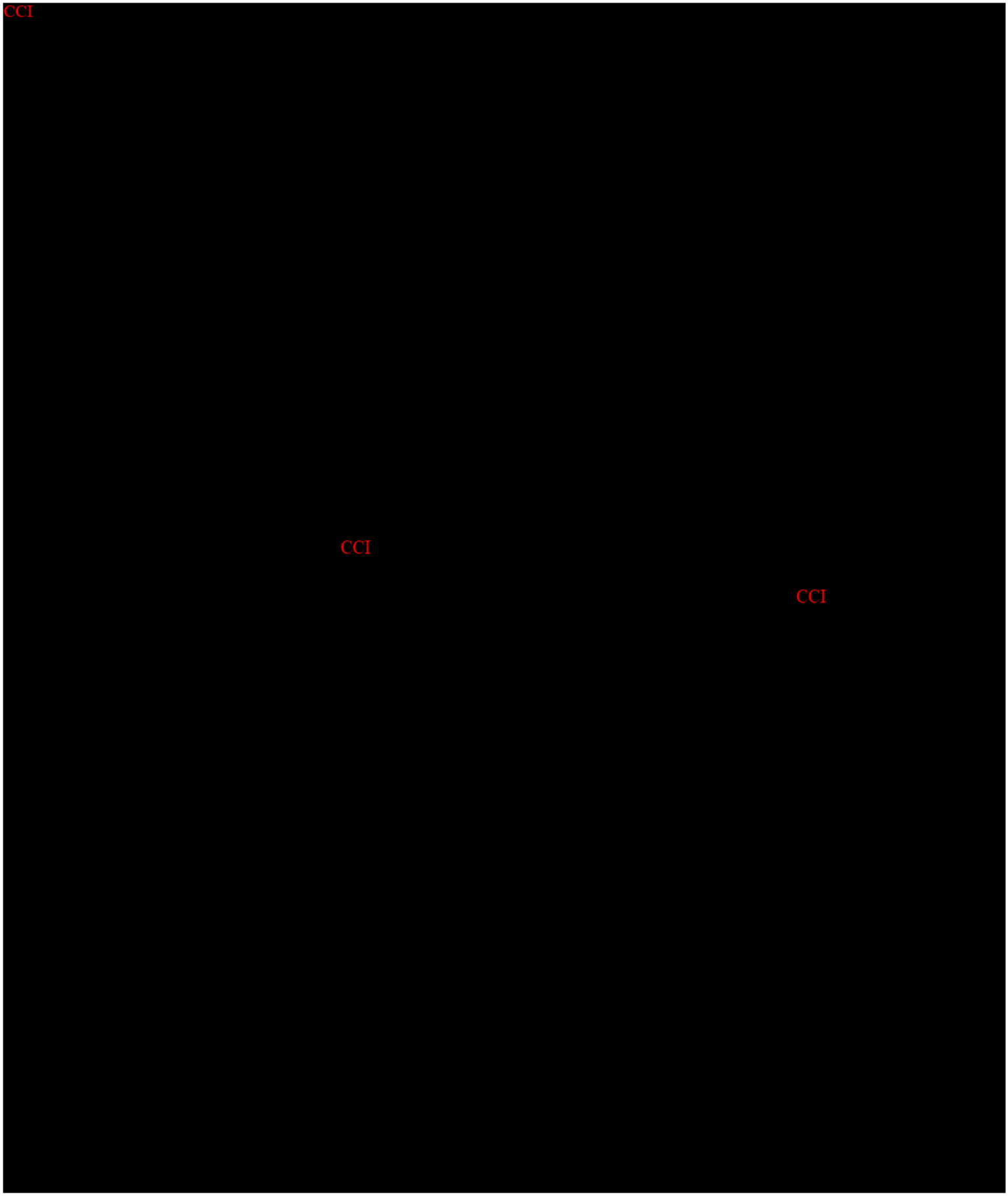
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