# PROTOCOL

## 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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|---|---|
| **Short Title:** | **S**ARS-CoV-2: **P**hase III T**R**ial of **I**nhaled I**NTER**feron-β Therapy |
| **Trial Name:** | SPRINTER |
| **Compound:** | IFN-β1a (for inhalation) |
| **Compound Name:** | SNG001 |
| **EudraCT Number:** | 2020-004743-83 |
| **Protocol Number:** | SG018 |
| **Version and Date:** | 5, 09 September 2021 |

**Previous Document History:**

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# SYNAIRGEN RESEARCH LTD

# CLINICAL STUDY PROTOCOL SG018

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|---|---|
| **Study Title:** | 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 |
| **Protocol Number:** | SG018 |
| **Investigational Product:** | SNG001 (IFN-β1a for inhalation) |
| **Sponsor:** | Synairgen Research Ltd<br>Level F (810) South Block, Southampton General Hospital<br>Tremona Road, Southampton, SO16 6YD, UK |
| **Development Phase:** | Phase III |
| **Sponsor's Medical Monitor:** | PPD |
| **Chief Investigator:** | PPD |

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## STUDY PROTOCOL SG018 - PROTOCOL SIGNATURE PAGE

## SPONSOR REPRESENTATIVE

I have reviewed and agreed this protocol and its contents. My signature, in conjunction with the signatures of the Sponsor's Medical Officer, the Chief Investigator, confirms the agreement of all parties that the clinical trial will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Council on Harmonisation Guideline for Good Clinical Practice (ICH GCP), the standards set out by the UK Policy Framework for Health and Social Care Research, The UK Medicines for Human Use (Clinical Trials) Regulations 2004 and associated amendments, the EU Clinical Trials Directive 2001/20/EC, the EU GCP Directive 2005/28/EC, the Clinical Trial Regulation (EU) No 536/2014**,** the US Federal Regulations, including but not limited to 21CFR and the Ethical principles that have their origin in the Declaration of Helsinki.

Signature: PPD

Name (PRINT): PPD

Title: PPD

Date of signature: PPD

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## STUDY PROTOCOL SG018 - PROTOCOL SIGNATURE PAGE

### SPONSOR'S MEDICAL OFFICER

I have reviewed and agreed this protocol and its contents on behalf of the Sponsor. My signature, in conjunction with the signatures of the Sponsor Representative, the Chief Investigator, confirms the agreement of all parties that the research study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Council on Harmonisation Guideline for Good Clinical Practice (ICH GCP), the standards set out by the UK Policy Framework for Health and Social Care Research, The UK Medicines for Human Use (Clinical Trials) Regulations 2004 and associated amendments, the EU Clinical Trials Directive 2001/20/EC, the EU GCP Directive 2005/28/EC, the Clinical Trial Regulation (EU) No 536/2014, the US Federal Regulations, including but not limited to 21CFR and the Ethical principles that have their origin in the Declaration of Helsinki.

Signature: DocuSigned by: PPD

Name (PRINT): PPD

Title: PPD

Date of signature: PPD

## SYNAIRGEN RESEARCH LTD

## CLINICAL STUDY PROTOCOL SG018 - PROTOCOL SIGNATURE PAGE

## CHIEF INVESTIGATOR

I have reviewed and agreed this protocol and its contents. My signature, in conjunction with the signatures of the Sponsor Representative, Sponsor's Medical Officer, confirms the agreement of all parties that the clinical trial will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Council on Harmonisation Guideline for Good Clinical Practice (ICH GCP), the standards set out by the UK Policy Framework for Health and Social Care Research, The UK Medicines for Human Use (Clinical Trials) Regulations 2004 and associated amendments, the EU Clinical Trials Directive 2001/20/EC, the EU GCP Directive 2005/28/EC, the Clinical Trial Regulation (EU) No 536/2014, the US Federal Regulations, including but not limited to 21CFR and the Ethical principles that have their origin in the Declaration of Helsinki.

Signature: DocuSigned by: PPD

Name (PRINT): PPD

Title: PPD

Date of signature: PPD

**SYNAIRGEN RESEARCH LTD**

**CLINICAL STUDY PROTOCOL SG018 - PROTOCOL SIGNATURE PAGE**

**PRINCIPAL INVESTIGATOR**

I confirm that I have read and agreed this protocol and its contents. I understand that all information concerning SNG001 and this protocol supplied to me by Synairgen Research Ltd is confidential.

My signature below confirms that as part of my responsibility as Principal Investigator, I will ensure that the clinical trial is conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Council on Harmonisation Guideline for Good Clinical Practice (ICH GCP), the standards set out by the UK Policy Framework for Health and Social Care Research, The UK Medicines for Human Use (Clinical Trials) Regulations 2004 and associated amendments, the EU Clinical Trials Directive 2001/20/EC, the EU GCP Directive 2005/28/EC, the Clinical Trial Regulation (EU) No 536/2014, the US Federal Regulations, including but not limited to 21CFR and the Ethical principles that have their origin in the Declaration of Helsinki.

Signature:

Name (PRINT): _____

Title: _____

Date of signature: _____

## PROTOCOL SYNOPSIS

**Study Title:**

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

**Protocol number:** SG018

**Study centres:** Multi-national and multicentre

**Number of randomised patients:**
At least 610 randomised patients in total, randomised 1:1 to the following arms:

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

*Each syringe contains CCI mL of SNG001 nebuliser solution, containing CCI MIU/mL of interferon beta-1a (IFN-β)
+Each syringe contains CCI mL of formulation buffer

| **Study period:** 2020 onwards | **Phase of development**: Phase III |
|---|---|

**Background:**

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) is a global threat and there is a need to assess new treatments which will prevent and effectively treat severe lower respiratory tract (LRT) illness caused by the SARS-CoV-2.

IFN-β has showed antiviral activity against SARS-CoV-2 in cell-based assays (1). IFN-β driven anti-viral responses have been shown to be compromised/deficient in older people (2) and those with chronic airways diseases (3, 4). These, and other patient groups are at high risk of developing severe LRT illness which can be fatal (5). The IFN-β deficiency can be overcome through the administration of exogenous IFN-β. This has been shown both *in vitro*, using cells from patients, and in clinical trials using SNG001 (an inhaled IFN-β1a formulation for nebulisation). We hypothesise that SNG001 will rectify the deficiency in the lungs in at-risk patients and prevent severe LRT illness in the context of SARS-CoV-2 infection.

The SG016 hospital pilot study was completed in May 2020. During this pilot study, 101 hospitalised adults, ≥18 years of age, with confirmed or suspected SARS-CoV-2 infection were randomised to receive SNG001 or placebo. Results of the pilot study showed that the risks of developing severe COVID-19 (the disease caused by SARS-CoV-2) were markedly reduced in patients receiving SNG001 compared to placebo and additionally that patients who received SNG001 were more than twice as likely to recover from COVID-19 as those on placebo. In addition, there was a significant reduction in breathlessness in patients receiving SNG001, compared to placebo (6).

SNG001 has been well tolerated in all clinical studies to date. Around 401 patients have been treated with SNG001. Of the 401 patients, approximately 67 patients had chronic obstructive pulmonary disease (COPD), 166 patients had confirmed COVID-19 with varying underlying diseases i.e. heart disease, lung disease, diabetes etc and the remaining 168 patients had

asthma. The majority of the 401 patients had or were suspected to have an active respiratory viral infection (rhinovirus, influenza, coronavirus, SARS-CoV-2, etc) at the time of randomisation.

SNG001 is pH neutral, rather than acidic and does not contain excipients such as mannitol, human serum albumin (HSA) and arginine, which are present in the injectable IFN-β formulations and which may have their own unwanted effects if delivered to the lungs.

SNG001 has historically been delivered using the CCI, a mesh nebuliser made by CCI CCI. The CCI has been tested to ensure the drug retains its activity after aerosolisation. A dose escalating trial established a target lung dose which induced an antiviral response in the lungs that was present 24 hours after dose administration.

In this trial the CCI CCI device will be used. The CCI is mesh nebuliser that is widely available and is better suited to single patient usage in the hospital setting. Laboratory assessments found that both the CCI and the CCI had similar levels of protein content in and similar IFN-β activity post nebulisation.

The primary endpoints are to evaluate time to hospital discharge and time to recovery in patients with confirmed SARS-CoV-2 infection who are hospitalised due to moderate COVID-19, after administration of SNG001 compared to placebo, where moderate COVID-19 is defined as presence of clinical signs and symptoms necessitating administration of oxygen therapy by mask or nasal prongs and recovery is defined as no limitation of activities according to the World Health Organization (WHO) Ordinal Scale of Clinical Improvement (OSCI), with no rebound at subsequent assessments. The WHO OSCI to be used in this trial is the 18 February 2020 version as recommended by the WHO (7).

**Purpose of the study:** The purpose of this Phase III study is to confirm that SNG001 can accelerate the recovery of hospitalised patients receiving oxygen with confirmed SARS-CoV-2. Safety and other efficacy endpoints will also be assessed.

**Study Population:**
Adults, ≥18 years of age with 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 validated 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]) or endotracheal intubation and invasive mechanical ventilation.

**Study Design:**

Eligible patients will be randomised in a 1:1 ratio to receive SNG001 two syringes or placebo two syringes.

Patients who have a positive virus test for SARS-CoV-2 prior to hospitalisation will be randomised no later than 48 hours after hospital admission. If the virus test is performed more than 96 hours prior to hospitalisation, the test will have to be repeated in the hospital prior to randomisation. Only patients whose repeated virus test is positive will be randomised, no later than 48 hours after confirmation of SARS-CoV-2 infection.

Patients who have their first positive virus test for SARS-CoV-2 after hospitalisation will be randomised no later than 48 hours after confirmation of SARS-CoV-2 infection. SNG001 or placebo will be administered via the CCI nebuliser. Patients will receive a dose of SNG001 or placebo once a day for 14 days and will be followed up for up to 90 days after the first dose of study medication (or randomisation date if the patient is not dosed). Study data will be collected from patients daily, as per the study schedule. Efficacy will be determined though differences between the groups in the WHO OSCI scores, and the secondary endpoints. Adverse events (AEs) and concomitant medications will be monitored throughout the study period.

A Data Safety Monitoring Committee (DSMC) will perform a review of the safety data before 100 patients complete study treatment, to ensure the safety of study patients. The DSMC will also meet as and when necessary, i.e. if a safety issue arises or when the DSMC requests a further meeting.

**Study Objectives**

**Primary Objective:**

To evaluate recovery in patients with moderate COVID-19 after administration of SNG001 compared to placebo.

**Secondary Objectives:**

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

**Exploratory objective:**

CCI

**Study Endpoints**

**Primary Endpoints:**

a. Time to hospital discharge, defined by the WHO OSCI score of 2 or below, with no rebound at subsequent assessments.
b. Time to recovery, where recovery is defined as the WHO OSCI score of 1 or below, with no rebound at subsequent assessments.

**Key Secondary Endpoints:**

a. Progression to severe disease or death, defined by the WHO OSCI score of 5 or above within 35 days of first dose (or randomisation date if the patient is not dosed).
b. Progression to intubation or death, defined by the WHO OSCI score of 6 or above within 35 days of first dose (or randomisation date if the patient is not dosed).
c. Death within 35 days of first dose (or randomisation date if the patient is not dosed).

**Secondary Endpoints:**

a. 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.
b. Hospital discharge by Days 7, 14, 21 and 28.
c. Improvement across the entire WHO OSCI by Days 7, 14, 21 and 28.
d. Changes in breathlessness, cough and sputum scale (BCSS) score during the study

period, including disaggregated breathlessness and cough scores.
e. Changes in National Early Warning Score 2 (NEWS2) during the hospitalisation period.
f. Daily assessment of COVID-19 symptoms and limitation of usual activities.
g. Quality of life measured using EQ-5D-5L.
h. Long-COVID-19 symptoms.
i. Safety and tolerability – vital signs, AEs, concomitant medications, and immunogenicity.

**Exploratory Endpoint:**

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**Inclusion criteria:**

To be eligible for randomisation into this study, each patient must fulfil the following criteria:

1. Male or female, ≥18 years of age at the time of consent.
2. Admitted to hospital due to the severity of their COVID-19.[1]
3. Positive virus test for SARS-CoV-2 using a validated molecular assay or antigen assay. Patients who had a positive virus test for SARS-CoV-2 prior to hospitalisation will be randomised no later than 48 hours after hospital admission. If the virus test is performed more than 96 hours prior to hospitalisation, the test will have to be repeated in the hospital prior to randomisation. Only patients whose repeated virus test is positive will be randomised, no later than 48 hours after confirmation of SARS-CoV-2 infection.
   Patients who had their first positive virus test for SARS-CoV-2 after hospitalisation will be randomised no later than 48 hours after confirmation of SARS-CoV-2 infection.
4. Require oxygen therapy via nasal prongs or mask (WHO OSCI score of 4).
5. Provided informed consent.
6. Female patients must be ≥1 year post-menopausal, surgically sterile, or using a highly effective method of contraception. Acceptable highly effective methods of contraception include;
   - bilateral tubal occlusion
   - intrauterine device (provided coils are copper-banded)
   - levonorgestrel intrauterine system (e.g., Mirena™)
   - medroxyprogesterone injections (e.g., Depo-Provera™)
   - etonogestrel implants (e.g., Implanon™, Norplan™)
   - normal and low dose combined oral pills
   - norelgestromin/ ethinylestradiol transdermal system

[1] Patients admitted to the hospital for reasons that are non-COVID-19 related, who subsequently develop clinical symptoms of COVID-19, test positive for SARS-CoV-2, and require prolongation of their hospital admission, as a consequence of COVID-19, and require treatment with supplemental oxygen (via nasal prongs or mask), must be discussed with the Sponsor's medical monitor prior to randomisation to assess suitability for the trial.

- intravaginal device (e.g., ethinylestradiol and etonogestrel), desogestrel (e.g., Cerazette™)
- total sexual abstinence (defined as refraining from heterosexual intercourse)
- vasectomised sexual partner.

Women of childbearing potential should have been stable on their chosen method of birth control for a minimum of 3 months before entering the trial and should continue with birth control for 1 month after the last dose of inhaled IFN-β1a/matching placebo. In addition to the highly effective method of contraception (except for the practice of total sexual abstinence), a condom (in UK with spermicides) should be used by the male partner for sexual intercourse from randomisation (Visit 2) and for 1 month after the last dose of inhaled IFN-β1a/matching placebo to prevent pregnancy.

7. Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered post-menopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age specific requirements apply:

    - Women <50 years old would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and if follicle stimulating hormone (FSH) levels are in the postmenopausal range.
    - Women ≥50 years old would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

    If, in the setting of the pandemic, the use of an acceptable birth control method is not possible, the decision to enrol a woman of childbearing potential should be based on the benefit-risk for the patient, which should be discussed with the patient at the time of the informed consent.

**Exclusion Criteria:**

A patient must not be randomised into the study if they meet any of the following criteria:

1. Evidence of ongoing SARS-CoV-2 infection for more than 3 weeks, confirmed by a validated molecular assay or validated antigen assay.
2. Non-invasive ventilation (CPAP/BiPAP) or high-flow nasal oxygen therapy (WHO OSCI score of 5).
3. Endotracheal intubation and invasive mechanical ventilation (WHO OSCI score of ≥6) or admission to intensive care.
4. Previous SARS-CoV-2 infection confirmed by a validated molecular assay or validated antigen assay.
5. Any condition, including findings in the patients' medical history or in the pre-randomisation study assessments that in the opinion of the Investigator, constitute a risk or a contraindication for the participation of the patient into the study or that could interfere with the study objectives, conduct or evaluation.
6. Participation in previous clinical trials of SNG001.
7. Current or previous participation in another clinical trial where the patient has received a dose of an Investigational Medicinal Product (IMP) containing small molecules

within 30 days or 5 half-lives (whichever is longer) prior to entry into this study or containing biologicals within 3 months prior to entry into this study.
8. Inability to use a nebuliser with a mouthpiece.
9. Inability to comply with the requirements for storage conditions of study medication in the home setting.
10. History of hypersensitivity to natural or recombinant IFN-β or to any of the excipients in the drug preparation.
11. Females who are breast-feeding, lactating, pregnant or intending to become pregnant.

**Test product, dose, and mode of administration:** SNG001 nebuliser solution is presented in glass syringes containing CCI mL of drug product solution at a concentration of CCI MIU/ml.

The CCI device will be filled with the contents of two syringes (if randomised to Arm 1). Patients will inhale study medication once a day.

During administration of SNG001, study sites should ensure they adhere to any local requirements and guidelines for performing inhalation in patients with COVID-19.

**Reference product, dose and mode of administration:** The placebo will be the same formulation as the study medication but without IFN-β1a (i.e. only the excipients of the SNG001 solution).

The CCI device will be filled with the contents of two syringes (if randomised to Arm 2). Patients will inhale study medication (placebo) once a day.

During administration of placebo, study sites should ensure they adhere to any local requirements and guidelines for performing inhalation in patients with COVID-19.

**Duration of Treatment:** Patients will receive study medication for 14 days.

**Sample Size:** Success will be determined if at least one of the primary endpoints is declared statistically significant by the primary analysis. A sample size of 610 patients in total using a 1:1 randomisation ratio (305 patients 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 allows for an interim analysis to assess futility.

**Statistical Methods**

**Analysis populations**

The intention-to-treat (ITT) population is defined as all randomised patients.

The safety population will include all randomised patients who receive at least one dose of study drug.

The per protocol population will include all patients in the ITT population who do not have any protocol deviations with an impact on efficacy on or prior to Day 35.

The PK population will include all patients in the safety population who have at least one valid PK concentration measurement available.

**Statistical analysis methodology**

The same method of analysis will be used for both primary endpoints. The primary analysis will use a Cox proportional hazards model. Patients who die will be administratively censored at Day 28, i.e. time to hospital discharge and time to recovery for these patients will be fixed at 28 days. Patients who neither recover nor die will be censored at the date of their last WHO OSCI assessment.

For the key secondary endpoint (progression to severe disease or death) a logistic regression model will be used to estimate the difference in probabilities between the treatment groups.

Safety analyses will be based primarily on AE information which will be summarised descriptively, including summary of treatment-emergent AEs.

CCI [redacted]

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**Estimands**

**Primary Estimand**

The first 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 the table below.

| 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 | Treatment policy: The time to hospital discharge will be used regardless of study withdrawal and regardless of the duration of follow-up following hospital discharge. This assumes relapse is independent to the treatment effect. |
| 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. |

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 the table below.

| **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 | Treatment policy: The time to recovery will be used regardless of study withdrawal and regardless of the duration of follow-up following recovery. This assumes relapse is independent to the treatment effect. |
| 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. |

**Key Secondary Estimands**

The first 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 (or randomisation date if the patient is not dosed) of patients in the ITT population. Intercurrent events will be handled as follows:

| **Intercurrent event** | **Policy** |
|---|---|
| Death | Composite variable: The definition of severe disease includes patients who die within 35 days of first dose (or randomisation date if the patient is not dosed), regardless of their WHO 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. |

The second 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 (or randomisation date if the patient is not dosed) of patients in the ITT population.

The third key secondary estimand will be the difference in probabilities for SNG001 versus placebo for death within 35 days of first dose (or randomisation date if the patient is not dosed) of patients in the ITT population. For both the second and third key secondary endpoints the same policies will be used for handling intercurrent events as progression to severe disease or death.

**Interim Analyses**

An unblinded interim analysis will be conducted by an independent team 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. If feasible, it is planned to assess futility on the first 300 randomised patients once all of these patients have completed the Day 35 visit or have withdrawn from the study. The primary analyses for the two primary endpoints will be conducted for the interim analysis and provided to an Independent Data Monitoring Committee (IDMC).

## Study Schedule

| Assessment | Pre-Treatment[1] | Treatment Phase[2] | End of Treatment | Follow-up | | |
|---|---|---|---|---|---|---|
| | Day 0 | Days 1 to 14 | Day 15 | Day 16 to Day 28 | Day 29 to Day 35 | Day 36 to Day 90 |
| Informed consent | X | | | | | |
| Inclusion / Exclusion criteria | X | | | | | |
| Medical history | X | | | | | |
| COVID-19 infection history[3] | X | | | | | |
| Patient demographics | X | | | | | |
| Physical examination[4] | X[5] | X[5, 6] | X[5, 6] | | | |
| Height and weight | X | | | | | |
| WHO Ordinal Scale of Clinical Improvement[4] | X | X[7, 8] | X[7, 8] | X[7, 8] | X[7, 8] | |
| BCSS | X | X[7, 8] | X[7, 8] | X[7, 8] | | X[7,8, 9] |
| Vital signs[4, 10] | X | X[6] | X[6] | | | |
| NEWS2[11] | X | X[6] | X[6] | X[6] | | |
| EQ-5D-5L | X[12] | X[7, 8, 14] | X[7, 8, 12, 13] | X[7, 8, 14] | X[7, 8, 14] | X[7, 8, 9] |
| COVID-19 symptom assessment | | X[7, 8] | X[7, 8] | X[7] | X[7, 8] | X[7, 8, 9] |
| Long-COVID-19 assessments | | | X[7, 8] | X[7, 8, 15] | | X[7, 8, 9] |
| Urine pregnancy test (if applicable) | X | | | | | |
| Device training (if required) | X | X | | | | |
| Randomisation | X | | | | | |
| Blood samples for immunogenicity test[16] | X | | | | | X[17] |
| Dose administration | | X[18] | | | | |
| Recording of AEs and SAEs[19] | X | X[7, 8] | X[7, 8] | X[7, 8] | X[7, 8] | X[7, 8, 20] |
| Recording of concomitant medications | X | X[7, 8] | X[7, 8] | X[7, 8] | X[7, 8] | X[7, 8] |
| CCI [redacted] | | X[22] | | | | |

1. Dosing may start on the same day as the pre-treatment assessments and if so the Day 1 assessments will not be performed.
2. All assessments and sampling are to be carried out pre-dose.
3. To include symptoms experienced within the preceding 24 hours and SARS-CoV-2 variant information (if available).
4. Physical examination, vital signs, and Ordinal Scale of Clinical Improvement assessments should be conducted together at approximately the same time each day.
5. Includes chest examination only unless a physical examination is deemed necessary by the Investigator.
6. Hospitalised patients only.
7. For patients who have been discharged, assessments should be performed via phone/video link.
8. Patients who stop dosing (for example if they become ventilated or for any other reason) should undergo these key data assessments, if possible.
9. Day 60 (-2 to +5 days) and Day 90 (-2 to +5 days) only.
10. Includes daily temperature, respiratory rate, heart rate and blood pressure.

11. The highest NEWS2 score for each calendar day should be collected. This will be assessed in hospital only during treatment and follow-up.
12. Complete EQ-5D-5L questionnaire.
13. If the EQ-5D-5L assessment is missed on Day 15, it may be completed on Day 16.
14. Complete EQ-5D-5L questionnaire on Day 7 and Day 28 only. The mobility, self-care and usual activities dimensions of the questionnaire will be assessed daily from Day 1 to Day 35.
15. Day 28 only.
16. All sites/patients, where collection is feasible.
17. Day 44 (+/-5 days) only
18. During administration of study drug, study sites should ensure they adhere to any local requirements and guidelines for performing inhalation in patients with COVID-19.
19. See Sections 7.7.1 and 7.8 for AE and SAE reporting requirements.
20. For details regarding AE and SAE collection during Days 36 to 90, please see Section 5.3.4.
21. CCI [redacted]
22. CCI [redacted]

## TABLE OF CONTENTS

## ABBREVIATIONS AND DEFINITIONS

| Abbreviation/Terms | Definition |
|---|---|
| ADA | Anti-drug antibody |
| AE | Adverse Event |
| CCI | CCI |
| BCSS | Breathlessness, Cough and Sputum Scale |
| BiPAP | Bilevel Positive Airway Pressure |
| BMI | Body Mass Index |
| CI | Confidence Interval |
| CCI | CCI |
| COPD | Chronic Obstructive Pulmonary Disease |
| COVID-19 | Disease caused by SARS-CoV-2 |
| CPAP | Continuous Positive Airway Pressure |
| CRA | Clinical Research Associate |
| CRO | Clinical Research Organisation |
| Delegate | A qualified member of the study team delegated to perform a task by the investigator |
| DSMC | Data Safety Monitoring Committee |
| eCRF | Electronic Case Report Form |
| EQ-5D-5L | EuroQuol 5-dimension 5-level (quality of life questionnaire) |
| FACIT | Functional Assessment of Chronic Illness Therapy |
| FDA | U.S. Food and Drug Administration |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| FSH | Follicle Stimulating Hormone |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| HSA | Human Serum Albumin |
| IB | Investigator's Brochure |
| ICH | International Council for Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IFN-β | Interferon-beta |
| IMP | Investigational Medicinal Product |
| IRB | Institutional Review Board |
| ITT | Intention-to-treat |
| LRT | Lower Respiratory Tract |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MIU | Million International Units |
| MMRM | Mixed Models with Repeated Measures |
| NEWS2 | National Early Warning Score 2 |
| NOAEL | No-observed-adverse-effect-level |
| Placebo | Comparator Medication Without the Active Ingredient |
| R&D | Research and Development |
| Randomisation | Random Allocation to Treatment Group |

| | |
|---|---|
| REC | Research Ethics Committee |
| RTI | Respiratory Tract Infection |
| RT-PCR | Reverse Transcription Polymerase Chain Reaction |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome-Coronavirus 2 |
| SOC | Standard of Care |
| Source data | Original documents, data and record (including but not limited to: hospital records, source documents, lab reports) |
| Sponsor | Company that takes responsibility for the initiation, management and financing of the trial: Synairgen Research Limited |
| TEAE | Treatment-Emergent Adverse Event |
| CCI | CCI |
| VAS | Visual Analogue Scale |
| WHO | World Health Organization |

# 1 INTRODUCTION

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) is a global threat and there is a need to assess new treatments which will prevent and effectively treat severe lower respiratory tract (LRT) illness caused by the SARS-CoV-2 virus.

Interferon beta (IFN-β) has showed antiviral activity against SARS-CoV-2 in cell-based assays (1). IFN-β driven anti-viral responses have been shown to be compromised/deficient in older people (2) and those with chronic airways diseases (3, 4). These, and other patient groups are at high risk of developing severe LRT illness which can be fatal (5). The IFN-β deficiency can be overcome or boosted through the administration of exogenous IFN-β. This has been shown both *in vitro*, using cells from patients, and in clinical trials using SNG001 (an inhaled IFN-β1a formulation for nebulisation). We hypothesise that SNG001 will rectify the deficiency in the lungs in at-risk patients and prevent severe LRT illness in the context of SARS-CoV-2 infection.

The SG016 hospital pilot study was completed in May 2020. During this pilot study, 101 hospitalised adults, ≥18 years of age, with confirmed or suspected SARS-CoV-2 infection were randomised to receive SNG001 or placebo. Results of the pilot study showed that the risks of developing severe COVID-19 (the disease caused by SARS-CoV-2) were markedly reduced in patients receiving SNG001 compared to those receiving placebo and that patients who received SNG001 were more than twice as likely to recover from COVID-19 as those on placebo. In addition, there was a significant reduction in breathlessness in patients receiving SNG001, compared to placebo (6).

SNG001 has been well tolerated in all clinical studies to date. Around 401 patients have been treated with SNG001. Of these, approximately 67 patients had chronic obstructive pulmonary disease (COPD), 166 patients had confirmed COVID-19 with varying underlying diseases i.e. heart disease, lung disease, diabetes etc and the remaining 168 patients had asthma. The majority of these 401 patients had or were suspected to have an active respiratory viral infection (rhinovirus, influenza, coronavirus, SARS-CoV-2, etc) at the time of randomisation.

SNG001 is pH neutral, rather than acidic and does not contain excipients such as mannitol, human serum albumin (HSA) and arginine, which are present in the injectable IFN-β formulations and which may have their own unwanted effects if delivered to the lungs.

SNG001 has historically been delivered using the CCI, a mesh nebuliser made by CCI CCI. The CCI has been tested to ensure the drug retains its activity after aerosolisation. A dose escalating trial established a target lung dose which induced an antiviral response in the lungs that was present 24 hours after dose administration.

This SG018 trial is designed to assess the efficacy of a 2 syringe dose of SNG001 delivered by the CCI nebulizer. Two syringes in the CCI are predicted to deliver a lung dose of approximately CCI MIU, which is approximately 32% higher than has historically been delivered by the CCI (CCI MIU).

The rationale for the slightly higher dose administered with the CCI nebulizer is based on the non-clinical data that support a maximum administered lung dose per day to humans of CCI µg (CCI MIU), assuming a conservative 60 kg human body weight. This dose is based on the no-observed-adverse-effect-level (NOAEL) from the Good Laboratory Practice (GLP) repeat dose 14-day toxicity study in cynomolgus monkey of CCI µg/kg/day total inhaled dose,

which corresponds to CCI µg/kg/day lung deposited dose, assuming a lung deposition fraction of 25%. The maximum dose that will be administered to patients in this study from the two syringes of SNG001 will be CCI µg (CCI MIU) per day. The dose of CCI µg (CCI MIU) represents the emitted dose from the CCI nebulizer and therefore, the proportion of drug delivered to the lung will be lower. The estimated administered lung dose with the CCI nebulizer will be 34.9% of the emitted dose of CCI µg (CCI MIU) and this equates to a lung dose of CCI µg (CCI MIU) (9). Safety margins of at least 4.2-fold between the NOAEL in the GLP toxicity study in monkeys and the dose of CCI µg/day (CCI MIU) administered in this study have been calculated, based on comparative lung exposure (mg/g lung) and using the U.S. Food and Drug Administration (FDA)-accepted method by Tepper et al. (10).

Safety of SNG001 has been investigated in 5 clinical studies, across a variety of patient populations including patients with asthma, patients with COPD and patients hospitalised due to severity of COVID-19. Treatment has been well tolerated, and no specific safety signals were observed, whether related to local tolerance or systemic effects. Based on the extensive experience from parenteral IFN-β1a administration, and negligible systemic exposure after administration of SNG001, clinically significant systemic events are not anticipated. The data from pre-clinical studies and the previous clinical trials with SNG001 do not indicate risk for local adverse effects in the lungs at the proposed doses.

The primary endpoints of this study are to evaluate time to hospital discharge and time to recovery in hospitalised patients receiving oxygen with confirmed SARS-CoV-2 infection after administration of SNG001 compared to placebo, where recovery is defined as the World Health Organization (WHO) Ordinal Scale of Clinical Improvement (OSCI) score of 1 or below, with no rebound at subsequent assessments. The OSCI to be used in this trial is the 18 February 2020 version as recommended by the WHO (7).

Complete information on SNG001 is available in the Investigator's Brochure (IB).

# 2 STUDY OBJECTIVES AND ENDPOINTS

## 2.1 Objectives

**Primary objective:**

To evaluate recovery in patients with moderate COVID-19 after administration of SNG001 compared to placebo.

**Secondary objectives:**

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

**Exploratory objective:**

CCI

## 2.2 Primary Endpoints:

a. Time to hospital discharge, defined by the WHO OSCI score of 2 or below, with no rebound at subsequent assessments.
b. Time to recovery, where recovery is defined as the WHO OSCI score of 1 or below, with no rebound at subsequent assessments.

## 2.3 Key Secondary Endpoint:

a. Progression to severe disease or death, defined by the WHO OSCI score of 5 or above within 35 days of first dose (or randomisation date if the patient is not dosed).
b. Progression to intubation or death, defined by the WHO OSCI score of 6 or above within 35 days of first dose (or randomisation date if the patient is not dosed).
c. Death within 35 days of first dose (or randomisation date if the patient is not dosed).

## 2.4 Secondary Endpoints:

a. 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.
b. Hospital discharge by Days 7, 14, 21 and 28.
c. Improvement across the entire WHO OSCI by Days 7, 14, 21 and 28.
d. Changes in breathlessness, cough and sputum scale (BCSS) score during the study period, including disaggregated breathlessness and cough scores.
e. Changes in National Early Warning Score (NEWS)2 during the hospitalisation period.
f. Daily assessment of COVID-19 symptoms and limitation of usual activities.
g. Quality of life measured using EuroQol 5-dimension 5-level (EQ-5D-5L).
h. Long-COVID-19 symptoms.
i. Safety and tolerability – vital signs, adverse events (AEs), concomitant medications, and immunogenicity.

## 2.5 Exploratory Endpoint:

CCI CCI CCI CCI

# 3 STUDY DESIGN

At least 610 adults, ≥18 years of age with 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. Potential study participants should be clinically assessed to ascertain whether interruptions and/or changes to oxygen delivery, to allow the administration of nebulised study drug, will be tolerated and not lead to significant hypoxia. Patients who are administered with oxygen via a mask can be switched to oxygen via nasal cannulae for the period of nebulised study drug delivery. Patients requiring high-flow nasal oxygen therapy, non-invasive ventilation (continuous positive airway pressure [CPAP]/bilevel positive airway pressure [BiPAP]) or endotracheal intubation during the Screening period are not eligible for this study. Patients will be randomised 1:1 to

receive SNG001 two syringes (approximately 305 patients) or placebo two syringes (approximately 305 patients).

Patients who have positive virus test for SARS-CoV-2 prior to hospitalisation will be randomised no later than 48 hours after hospital admission. If the virus test is performed more than 96 hours prior to hospitalisation, the test will have to be repeated in the hospital prior to randomisation. Only patients whose repeated virus test is positive will be randomised, no later than 48 hours after confirmation of SARS-CoV-2 infection.

Patients who have their first positive virus test for SARS-CoV-2 after hospitalisation will be randomised, no later than 48 hours after confirmation of SARS-CoV-2 infection.

SNG001 or placebo will be administered via the CCI nebuliser. Patients will receive a dose of SNG001 (two syringes) or placebo (two syringes) once a day for 14 days and will be followed for up to 90 days after the first dose of study medication (or randomisation date if the patient is not dosed). Study data will be collected from patients as per the study schedule. Efficacy will be determined though differences between the groups in the time to recovery and time to hospital discharge (primary endpoints), progression to severe disease or death, progression to intubation or death, and death within 35 days of the first dose (or randomisation date if the patient is not dosed; key secondary endpoints), as well as the secondary endpoints. AEs and concomitant medications will be monitored throughout the study period.

To ensure patient safety, a Data Safety Monitoring Committee (DSMC) will perform a review of the safety data before 100 patients complete study treatment, to ensure safety of study patients. The DSMC will also meet as and when necessary i.e. if a safety issue arises or when the DSMC requests a further meeting.

## 3.1 Criteria for Inclusion and Exclusion

### 3.1.1 Inclusion Criteria

To be eligible for randomisation into this study, each patient must fulfil the following criteria:

1. Male or female, ≥18 years of age at the time of consent.
2. Admitted to hospital due to the severity of their COVID-19[1].
3. Positive virus test for SARS-CoV-2 using a validated molecular assay or validated antigen assay.

   Patients who have a positive virus test for SARS-CoV-2 prior to hospitalisation will be randomised no later than 48 hours after hospital admission. If the virus test is performed more than 96 hours prior to hospitalisation, the test will have to be repeated in the hospital prior to randomisation. Only patients whose repeated virus test is positive will be randomised, no later than 48 hours after confirmation of SARS-CoV-2 infection.

[1] Patients admitted to the hospital for reasons that are non-COVID-19 related, who subsequently develop clinical symptoms of COVID-19, test positive for SARS-CoV-2, and require prolongation of their hospital admission, as a consequence of COVID-19, and require treatment with supplemental oxygen (via nasal prongs or mask), must be discussed with the Sponsor's medical monitor prior to randomisation, to assess suitability for the trial.

Patients who have their first positive virus test for SARS-CoV-2 after hospitalisation will be randomised, no later than 48 hours after confirmation of SARS-CoV-2 infection.

4. Require oxygen therapy via nasal prongs or mask (WHO OSCI score of 4).
5. Provided informed consent.
6. Female patients must be ≥1 year post-menopausal, surgically sterile, or using a highly effective method of contraception. Acceptable highly effective methods of contraception include;
    - bilateral tubal occlusion
    - intrauterine device (provided coils are copper-banded)
    - levonorgestrel intrauterine system (e.g., CCI )
    - medroxyprogesterone injections (e.g., CCI )
    - etonogestrel implants (e.g., CCI , CCI )
    - normal and low dose combined oral pills
    - norelgestromin/ ethinylestradiol transdermal system
    - intravaginal device (e.g., ethinylestradiol and etonogestrel), desogestrel (e.g., CCI )
    - total sexual abstinence (defined as refraining from heterosexual intercourse)
    - vasectomised sexual partner.

    Women of childbearing potential should have been stable on their chosen method of birth control for a minimum of 3 months before entering the trial and should continue with birth control for 1 month after the last dose of inhaled IFN-β1a/matching placebo. In addition to the highly effective method of contraception (except for the practice of total sexual abstinence), a condom (in UK with spermicides) should be used by the male partner for sexual intercourse from randomisation (Visit 2) and for 1 month after the last dose of inhaled IFN-β1a/matching placebo to prevent pregnancy.
7. Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered post-menopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age specific requirements apply:
    - Women <50 years old will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and if follicle stimulating hormone (FSH) levels are in the postmenopausal range.
    - Women ≥50 years old will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

    If, in the setting of the pandemic, the use of an acceptable birth control method is not possible, the decision to enrol a woman of childbearing potential should be based on the benefit-risk for the patient, which should be discussed with the patient at the time of the informed consent.

### 3.1.2 Exclusion Criteria

A patient must not be randomised into the study if they meet any of the following criteria:

1. Evidence of ongoing SARS-CoV-2 infection for more than 3 weeks, confirmed by a validated molecular assay or validated antigen assay.
2. Non-invasive ventilation (CPAP/BiPAP) or high-flow nasal oxygen therapy (WHO OSCI score of 5).
3. Endotracheal intubation and invasive mechanical ventilation (WHO OSCI score of ≥6) or admission to intensive care.
4. Previous SARS-CoV-2 infection confirmed by a validated molecular assay or validated antigen assay.
5. Any condition, including findings in the patient's medical history or in the pre-randomisation study assessments that in the opinion of the Investigator, constitute a risk or a contraindication for the participation of the patient into the study or that could interfere with the study objectives, conduct or evaluation.
6. Participation in previous clinical trials of SNG001.
7. Current or previous participation in another clinical trial where the patient has received a dose of an Investigational Medicinal Product (IMP) containing small molecules within 30 days or 5 half-lives (whichever is longer) prior to entry into this study or containing biologicals within 3 months prior to entry into this study.
8. Inability to use a nebuliser with a mouthpiece.
9. Inability to comply with the requirements for storage conditions of study medication in the home setting.
10. History of hypersensitivity to natural or recombinant IFN-β or to any of the excipients in the drug preparation.
11. Females who are breast-feeding, lactating, pregnant or intending to become pregnant.

# 4 STUDY MEDICATION

## 4.1 Allocation to Study Medication

Patients will be randomised to one of two groups (SNG001 or placebo) in a 1:1 ratio to receive SNG001 (two syringes [Arm 1]), or placebo (two syringes [Arm 2]), according to a pre-specified randomisation schedule in addition to Standard of Care (SOC).

Should a patient withdraw after randomisation, either prior to or after receiving any study medication, the randomisation number will not be re-assigned and the patient will not be replaced.

## 4.2 Breaking the Blind

The study will be patient- and investigator-blinded with regard to SNG001 or placebo but not the dose. Blinding codes should only be broken in emergency situations for reasons of patient safety. In the event of a need to unblind the patient the investigator (or delegate) will be able to access the patient randomisation list 24 hours a day.

A patient's assignment should only be unblinded in the case of an emergency where the knowledge of the study medication may influence further care of the patient. If a treatment code is unblinded for any reason, the Investigator will notify the Sponsor and a record will be kept of who unblinded the code, the reason for doing so, and the date and time the unblinding occurred. Every attempt will be made to minimise the number of people unblinded. Specific unblinding procedures and instructions can found in the Investigator Site File.

## 4.3 Stopping Rules

### 4.3.1 Individual Patient Stopping Rules

An individual patient will be discontinued permanently from the study medication for any one of the following reasons:

- The patient withdraws consent for study medication only.
- The patient is experiencing intolerable AEs.
- A protocol deviation has occurred that is deemed by the Investigator to put the patient at increased risk.
- The patient is not capable of taking the study medication.
- The Investigator/Sponsor feels that it is in the patient's best interest to be withdrawn from the study medication.
- Pregnancy.
- Other AEs reflecting a safety concern.
- The patient misses more than 4 consecutive doses (i.e. $5^{th}$ dose missed).
- Other (reason to be specified by the Investigator in the electronic case report form [eCRF]).

An individual patient will be discontinued permanently from the study i.e. from study treatment and data collection, for any one of the following reasons:

- The patient withdraws consent for taking part in the study.
- The patient is lost to follow-up.

### 4.3.2 Trial Stopping Rule

The trial will be terminated prematurely for any of the following reasons:

- In the opinion of the Sponsor or DSMC/Independent Data Monitoring Committee (IDMC), an unacceptable risk to the safety and welfare of patients is posed by the continuation of the study in light of review of the safety data.
- If clinically significant safety concerns arise within this trial or in any other trial with SNG001 which may impact on the wellbeing of patients in this trial.
- At individual sites, if the study procedures are not being performed according to Good Clinical Practice (GCP) and cannot be remedied or this is a serious breach.
- If recruitment is slow, at the Sponsor's discretion.
- Other (reason to be specified by the Sponsor).

If the trial is terminated prematurely, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

## 4.4 Description of Investigational Medicinal Product and Device

### 4.4.1 SNG001

The drug substance, recombinant IFN-β1a, is manufactured under Good Manufacturing Practice (GMP) conditions by CCI [redacted]. The drug product is manufactured under GMP conditions. The study medication is presented as a ready-to-use aqueous solution (neutral pH).

The IB contains further details of the composition of SNG001.

### 4.4.2 Placebo

The placebo will be the same formulation as the study medication but without IFN-β1a (i.e. only the excipients of the SNG001 solution). The IB contains further details of the composition of the placebo.

### 4.4.3 Inhalation Device

The study medication will be delivered using the CCI nebuliser. The CCI nebuliser is a portable mesh nebuliser marketed by CCI. CCI [redacted]

## 4.5 Dosage and Administration

While hospitalised, all patients will take their doses of study medication under the supervision of study staff. During administration of study medication, study sites should ensure they adhere to any local requirements and guidelines for performing inhalation in patients with COVID-19.

SNG001 nebuliser solution is presented in glass syringes containing CCI mL of drug product solution containing CCI MIU/mL of IFN-β1a. The CCI device should be filled with the contents of two syringes (if randomised to Arm 1).

The placebo nebuliser solution is presented in glass syringes containing CCI mL of solution containing only the excipients of the SNG001 solution. The CCI device should be filled with the contents of two syringes (if randomised to Arm 2) (See Appendix A).

If a patient requires supplemental oxygen during inhalation of the study medication, a nasal cannula can be used. Oxygen flow rate via a nasal cannula during study medication administration should not exceed CCI L/minute.

If oxygen supplementation using a nasal cannula during study medication administration is insufficient to ensure adequate oxygen saturation, additional oxygen can be provided by using both a nasal cannula and the oxygen port located on the bottom of the CCI CCI chamber. With this mode of oxygen supplementation, the oxygen flow rate via a nasal cannula should not exceed CCI L/minute and the flow rate to the CCI chamber should not exceed CCI L/minute.

Administration of study medication to patients receiving high-flow nasal oxygen therapy is not permitted as it is likely to result in suboptimal doses being delivered. However, patients receiving high-flow nasal oxygen therapy may, during administration of study medication, receive oxygen via a low-flow nasal cannula or CCI CCI chamber, as described above, if clinically tolerated.

Patients will inhale study medication once a day for 14 days. Administration of study medication should be carried out in compliance with any applicable local regulations for inhalation in COVID-19 patients.

The study medication should be removed from the fridge for a minimum of 15 minutes prior to taking the dose and for no longer than two hours.

Once patients have been randomised, resupply of study treatment can occur if the initial supply of study medication is damaged or unusable. Resupply should be attempted for patients who are between Day 1 and Day 12 and when the patient has not taken their Day 12 dose. If the patient has taken their Day 12 dose, they will not be resupplied for Days 13 and 14.

*For patients who have been discharged from hospital during the 14-day treatment phase:*

Patients will have been trained before discharge from hospital to fill the device with IMP and use it. Study staff will call (via telephone or video call) discharged patients on a daily basis and will be able to address any problems and answer any questions patients have about using the device.

If, after multiple training attempts, patients are not capable of taking the study medication at home, even with the support of study staff via phone or video link, they should be withdrawn from the study medication only. Study data should continue to be collected as per the study schedule.

### 4.5.1 Dose Delivery Times

It is anticipated that a dose of study medication will take 2 to 6 minutes to be delivered, depending on the patient's inhalation/exhalation breathing pattern.

### 4.5.2 Packaging and Labelling

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CCI

## 4.6 Preparation, Handling and Dispensing

### 4.6.1 Preparation Time

The study medication will not require reconstitution and will be supplied in pre-labelled syringes. Study medication will be put into the CCI nebuliser immediately prior to dosing.

### 4.6.2 Timing of Doses

The study medication should be taken once daily at approximately the same time of day. There must be a gap of at least 8 hours between doses (see Section 4.9 for the treatment of overdose).

### 4.6.3 Missed or Incomplete Doses

If a dose is missed or the complete dose is not taken, the following procedure must be followed:

1. Record in the source document and the eCRF that the dose has been missed/not completed with the reason why.

2. Continue with any remaining doses as normal (see Section 5.5 for patient withdrawal criteria).

## 4.7 Storage of Study Medication

Prior to dispensing, the study medication should be stored in a locked and temperature-controlled environment. The study medication should be stored between +2°C and +8°C. A daily temperature log must be kept to ensure that the study medication storage temperature is recorded. Any deviations from the storage conditions should be reported immediately to the Sponsor/Clinical Research Associate (CRA), and the study medication should be placed in quarantine and not used until authorisation has been given by the Sponsor to do so.

Patients who are discharged from hospital during the 14-day treatment phase should be instructed to keep the study medication in a refrigerator. Due to the stability data for the IMP, it is not necessary to keep a record of the fridge storage temperature at the patient's home.

Training will be given to the patients by study staff regarding storage of study medication, disposal of the syringes after they have been used to fill the device, what to do once they have completed all doses and any drug accountability that needs to be completed by the patient.

The study medication can be transported to the patient's home without the need for refrigeration. On arrival at the patient's home, the study medication should be placed in the refrigerator as soon as possible.

## 4.8 Drug Accountability

The Sponsor will provide the required documentation for study medication accountability, including reconciliation of drugs and maintenance of drug records.

The Investigator must maintain study medication accountability throughout the course of the study in accordance with regulatory requirements.

All patients who take the study medication whilst at home will either be asked to complete a drug accountability form after each dose of study medication or will be asked questions regarding it by study staff during their daily contact.

The amount of study medication received and dispensed to patients should be documented. Study medication dispensed to a patient should not be returned if unused. Patients will be given instructions for its disposal.

Drug accountability records will include:

- Confirmation and inventory of study medication delivery to the study site.
- An inventory of the study medication that has been provided to each patient.
- The serial number from the controller component of the CCI nebuliser device.
- Confirmation of administration of each dose of study medication.
- The return to the Sponsor or alternative disposition of unused products.

Dates of use, expiry dates, quantities, batch numbers, and the patient's randomisation and unique patient identification number should also be included on the accountability form.

Unused study medication must not be discarded without authority from the Sponsor or used for any purpose other than the present study.

During the study, where possible due to the nature of the study, the Sponsor (or delegate) will periodically review the drug accountability forms and check these against the actual study medication. Once the study has finished and the drug accountability forms have had a final check, the Sponsor (or delegate) will make arrangements for the return of the study medication or will authorise their destruction by the study site.

### 4.9 Treatment of Overdose

An overdose is defined as any dose greater than the once-a-day dose that is being used in this study i.e. two doses taken less than 8 hours apart. Any overdose must be recorded as a protocol deviation in the source documents.

In the event of overdose, if the patient is not in hospital, hospitalisation should be considered (if applicable) for observation and appropriate supportive treatment should be given. If the patient is in hospital, they should be observed and appropriate supportive treatment should be given. The Sponsor (or delegate) should be contacted in an expedient manner, whether associated with an AE (serious or non-serious) or not, to decide if the patient should continue in the study.

If the patient is experiencing AEs that may relate to an overdose of study medication, the IB should be consulted for details of any specific actions to be taken.

## 5 STUDY PROCEDURES

### 5.1 Patient Numbering

Every patient that gives informed consent will be logged and allocated a unique patient identification number. The unique patient identification number will consist of 9 digits (2 for the study number, 2 for the country, 2 for the site number and 3 for patient number), will be

assigned sequentially to each patient within each site and will identify the patient throughout the study.

## 5.2 Screening Failures

Screening failures are defined as patients who have given informed consent for the study, but who have not met the study Inclusion and/or the Exclusion Criteria. Re-screening of patients will be at the discretion of the Medical Monitor. If a patient is re-screened, they will be given a new patient identification number and must give informed consent again.

## 5.3 Study Visits

### 5.3.1 Pre-Treatment

*The following assessments should be performed on Day 0 prior to the first dose preferably in the following order:*

- Informed consent
- Inclusion/exclusion criteria
- Medical history
- COVID-19 infection history (SARS-CoV-2 variant information to also be collected if available)
- Patient demographics
- Physical examination (chest examination only unless a physical examination is deemed necessary by the Investigator)*
- WHO OSCI*
- Height and weight
- Vital signs (to include temperature, respiratory rate, heart rate and blood pressure)*
- BCSS
- NEWS2 (the highest NEWS2 score for each calendar day should be collected)
- EQ-5D-5L (complete questionnaire)
- Height and weight
- Urine pregnancy test, if applicable
- Check the patient will be able to use the nebuliser
- Randomisation
- Blood sample for immunogenicity test (all sites/patients, where collection is feasible)
- Recording of AEs, SAEs and concomitant medications

*Physical examination, WHO OSCI, and vital signs assessments should be conducted together at approximately the same time each day.

Eligibility to enter the study may be aided with data captured from SOC procedures and tests performed as part of the admission process.

Patients may take the first dose of study medication either on the same day as the pre-treatment assessments or the next day depending on timings. Day 1 is the day the first dose of study medication is taken. If Day 1 is the same as the day the pre-treatment assessments are performed then the Day 1 assessments do not need to be repeated.

### 5.3.2 Days 1 to 14

The following assessments should be performed daily from Day 1 to 14.

*For patients that remain in hospital the following assessments should be performed preferably in the following order:*

- WHO OSCI*
- Physical examination (chest examination only unless a physical examination is deemed necessary by the Investigator)*
- Vital signs (to include daily temperature, respiratory rate, heart rate and blood pressure)*
- BCSS
- EQ-5D-5L (complete questionnaire on Day 7 only. Mobility, self-care and usual activities dimensions from Day 1 to Day 14)
- COVID-19 symptom assessment
- NEWS2 (the highest NEWS2 score for each calendar day should be collected)
- Device training (if required)
- Administration of study medication
- Recording of AEs, SAEs and concomitant medications.

*Physical examination, WHO OSCI, and vital signs assessments should be conducted together at approximately the same time each day.

[redacted]
CCI [redacted]
CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

*For patients who have been discharged from hospital the following should be conducted over telephone/video call preferably in the following order:*

- WHO OSCI
- BCSS
- EQ-5D-5L (complete questionnaire on Day 7 only. Mobility, self-care and usual activities dimensions from Day 1 to Day 14)
- COVID-19 symptom assessment
- Device training (if required)
- Administration of study medication
- Recording of AEs, SAEs and concomitant medications

*If the patient has discontinued dosing and consents to data collection, attempts should be made to collect the following key data:*

- WHO OSCI
- BCSS
- EQ-5D-5L (complete questionnaire on Day 7 only. Mobility, self-care and usual activities dimensions from Day 1 to Day 14)
- COVID-19 symptom assessment
- Recording of AEs, SAEs and concomitant medications

### 5.3.3 End of Treatment

These assessments should be performed on Day 15 (see Sections 4.3.1 and 5.5).

*For patients that remain in hospital the following assessments should be performed, preferably in the following order:*

- WHO OSCI*
- Physical examination (chest examination only unless a physical examination is deemed necessary by the Investigator)*
- Vital signs*
- BCSS
- EQ-5D-5L (complete questionnaire)
- COVID-19 symptom assessment
- Long-COVID-19 assessment
- NEWS2 (the highest NEWS2 score for each calendar day should be collected)

- Recording of AEs, SAEs and concomitant medications.

*Physical examination, WHO OSCI, and vital signs assessments should be conducted together at approximately the same time each day.

*For patients who have been discharged from hospital the following should be conducted over telephone/video call preferably in the following order:*

- WHO OSCI
- BCSS
- EQ-5D-5L (complete questionnaire)
- COVID-19 symptom assessment
- Long-COVID-19 assessment
- Recording of AEs, SAEs and concomitant medications.

### 5.3.4 Follow-up

All follow-up assessments can be either done face-to-face if the patient remains in hospital or via telephone/video call if the patient has been discharged from hospital as per the study schedule.

**Days 16 to 28**

WHO OSCI, BCSS, the mobility, self-care and usual activities dimensions of EQ-5D-5L, NEWS2, COVID-19 symptoms, AEs, SAEs, and concomitant medications should continue to be collected on a daily basis from the patient. In addition, the EQ-5D-5L (complete questionnaire) should be completed and long- COVID-19 assessment should be performed on Day 28. For patients who have been discharged, assessments should be performed via telephone/video link, if possible.

NEWS2 will only be assessed if the patient remains in hospital. If the patient has been discharged from hospital NEWS2 will not be assessed. For hospitalised patients, if the components of NEWS2 have already been assessed on the day of the visit, this data can be used on the study to avoid the same procedures being conducted twice. The highest NEWS2 score for each calendar day should be collected.

**Days 29 to 35**

WHO OSCI, COVID-19 symptoms, the mobility, self-care and usual activities dimensions of EQ-5D-5L, AEs, SAEs, and concomitant medications should continue to be collected (as per Sections 7.7.1 and 7.7.2) on a daily basis until (and including) Day 35.

**Days 36 to 90**

Blood sample for immunogenicity testing should be obtained from the patient (all sites/patients, where collection is feasible) on Day 44 (+/- 5 days).

Updates to ongoing AEs and SAEs will be collected at Days 44, 60, and 90, and at any unscheduled study visits during this period as per Section 7.7.1 and 7.7.2.

New AEs and SAEs will be collected up to 28 days after the last dose of study medication and documented at the next scheduled or unscheduled study visits as per Section 7.7.1 and 7.7.2.

All concomitant medications will continue to be recorded until study completion.

In addition, BCSS, EQ-5D-5L (complete questionnaire), COVID-19 symptoms and long-COVID-19 assessments should be performed on Day 60 (-2 to +5 days) and Day 90 (-2 to +5 days).

## 5.4 Unscheduled Visits

The Investigator can request any of the study procedures described in the study schedule to be repeated as extra follow-up visits or to be added to a study visit where necessary. Unscheduled visits may be necessary if the patient is experiencing prolonged symptoms which the Investigator feels could be related to their study medication or if the Investigator is concerned about the patient's health. Unscheduled visits/study procedures should be captured in the source documents.

## 5.5 Patient Withdrawal

Patients may withdraw from the study at any time at their own request. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator should enquire about the reason for withdrawal, request that the patient disposes of all unused study medication (as instructed) and request the patient undergoes a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

Please refer to Section 4.3.1 for individual patient stopping rules.

If patient is withdrawn from the study or from the study medication, the reason for withdrawal will be documented in the source documents. If the patient is withdrawn from taking the study medication only but continues to give consent for data to be collected, the study schedule should be followed until Day 90.

**Lost to follow-up:**

Patients will be considered as lost to follow-up if no contact is made with the patient for at least 5 consecutive visits up to and including the Day 35 visit. A patient would also be considered lost to follow-up if no contact is made with the patient after the Day 35 visit and contact cannot be re-established up to and including the Day 90 visit. However, since maximum data collection for all patients is important to support the analyses of study endpoints, continued attempts to contact patients lost to follow-up should be made to allow completion of the follow-up assessments, wherever possible, up to the scheduled Day 90 visit. The status of 'lost to follow-up' should be amended in the CRF if patient contact is re-established and additional study follow-up data can be obtained.

For further guidance, see Appendix B.

# 6 STUDY ASSESSMENTS

## 6.1 Informed Consent

Informed consent will be obtained from the patient after the study has been fully explained and the patient has been given ample time to consider the study and discuss it in detail. The method of obtaining consent may vary due to the nature of this study. The method of obtaining and documenting the informed consent and the contents of the consent will comply with International Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP), and all applicable laws and regulations. Different methods, including written, verbal or electronic consent may be used. Each method will be discussed and approved by the Sponsor (or delegate) before the site takes the first consent. Whichever method is used informed consent will always be obtained from the patient prior to any study related procedures being performed. Informed consent must be obtained by a qualified medical doctor or nurse who have received study training.

If there is a new version of the patient information sheet and informed consent form, patients will be reconsented at their next study visit or, if they were already discharged from the hospital, they may be reconsented verbally over the phone/video link, or electronically. Patients will be informed as soon as possible of the changes and the Sponsor will determine whether the patients need to visit the site prior to their next study visit.

## 6.2 Medical History

The patient's medical history will be recorded in the source documents by the Investigator or their delegate to ensure the patient's eligibility.

The medical history should include, but is not limited to;

- Significant current and past medical history in the last 5 years, including hospitalisations, operations and medical history that affects inclusion and exclusion criteria (including sterilisation and contraception).
- Social history regarding smoking habits, alcohol consumption, drug allergies and medication use.
- For women, a menstrual history and history of contraception (if applicable).
- Vaccinations within 6 months prior to randomisation.

## 6.3 COVID-19 Infection History

The patient's COVID-19 infection history will be recorded in the source documents by a medical doctor or qualified nurse from the study team. Information regarding symptoms in the preceding 24 hours will be recorded.

A checklist/worksheet will be provided to study site staff to outline and help document the minimum symptoms to be assessed.

In addition, SARS-CoV-2 variant information will be collected (if available).

## 6.4 Patient Demography

Patient demographics will be recorded in the source documents. These will include age, sex, race/ethnicity and residence in care home, unless local laws or regulations do not permit this.

## 6.5 Physical Examination

A physical examination will be performed by a medical doctor on Day 0 or Day 1 prior to the first dose as per the study schedule.

Physical examinations may be repeated at various time points throughout the study, as clinically indicated.

If sites have difficulty in completing the chest examination due to risk of contamination/local policies, this will not be considered a protocol deviation, but will need to be explained in a file note. Height and weight will be recorded pre-treatment.

A checklist/worksheet will be available to study site staff to provide guidance on the physical examination. Results of the examinations will be recorded in the source documents.

## 6.6 Ordinal Scale for Clinical Improvement

The OSCI to be used in this trial is the 18 February 2020 version as recommended by the WHO (7).

**Ordinal Scale for Clinical Improvement**

| Patient State | Descriptor | Score |
|---|---|---|
| ***Uninfected*** | No clinical or virological evidence of infection | 0 |
| ***Ambulatory*** | No limitation of activities | 1 |
| | Limitation of activities | 2 |
| ***Hospitalised*** | Hospitalised, no oxygen therapy | 3 |
| | Oxygen by mask or nasal prongs | 4 |
| ***Hospitalised*** | Non-invasive ventilation or high-flow oxygen | 5 |
| | Intubation and mechanical ventilation | 6 |
| | Ventilation + additional organ support – pressors, RRT, ECMO | 7 |
| ***Dead*** | Death | 8 |

RRT – renal replacement therapy; ECMO - extracorporeal membrane oxygenation

The assessment should be carried out once a day at approximately the same time each day from Pre-treatment until Day 35. It is recommended that this assessment should be carried out by a clinically qualified member of the study team, i.e. a medical doctor or a qualified nurse. The assessment may be carried out face to face (before discharge) or over the phone/video link (post-discharge).

Patients' status on the day of hospital discharge should be assessed as ambulatory/uninfected (WHO OSCI score of 0, 1 or 2).

On the day of hospital discharge and on the days following hospital discharge, patients should be asked the following questions about their clinical status and return to the pre-COVID-19 level of activity:

- "In the past 24 hours, did you experience any signs or symptoms of your coronavirus infection?" "Yes" or "No" answer will be required.

- "In the past 24 hours, did you feel that your usual activities (e.g. work, study, housework, family or leisure activities) have returned to the level from before your coronavirus infection and did not require additional assistance/support*?" "Yes" or "No" answer will be required.

  * assistance/support is defined as additional help of other people and/or requirement for supplemental oxygen (or a higher level of supplemental oxygen), compared to the pre-COVID-19 state.

In order to minimise any potential influence on the patients, the interviewers will be required to read the questions to patients verbatim and not to change or interpret them in any way. The following scoring algorithm will be applied:

| **Presence of signs/symptoms of coronavirus infection (or virological evidence of infection)?** | **Usual activities returned to baseline level?** | **WHO OSCI score** |
|---|---|---|
| No | Yes | 0 |
| Yes | Yes | 1 |
| No | No | 2 |
| Yes | No | 2 |

The result of the OSCI assessment, from the day of hospital discharge, must be based upon the patient's responses to the 2 questions specified above and must not be adjusted based on the results from other outcome assessments (e.g. BCSS, brief pain inventory, long COVID-19 symptom assessment, and EQ-5D-5L), even if these data provide conflicting clinical information.

Repeated assessments of virological clearance in patients discharged from the hospital are not feasible within the study. Patients discharged from the hospital will be considered to have no virological evidence of infection unless a positive test is obtained.

The applicable WHO OSCI score and the date of assessment should be recorded in the source documents.

## 6.7 BCSS

The BCSS is a daily patient-reported outcome measure that was designed as a daily diary in which patients are asked to report the severity of three symptoms: breathlessness, cough and sputum (11).

Each symptom is represented by a single item which is evaluated on a 5-point scale ranging from 0-4, with higher scores indicating more severe symptoms. A mean decline of 1 point on the BCSS total scale signifies a substantial reduction in symptom severity. This questionnaire should only be completed if an approved translation in the language required by the patient is available. If an approved translation is not available, this assessment will not be conducted and will not be recorded as a protocol deviation.

This assessment should be carried once a day from Day 1 until Day 28 and then on Day 60 and Day 90 (see Appendix C).

- This assessment should be carried out at approximately the same time each day.
- This assessment should be completed via patient interview. Trained staff should read each question verbatim and ask the patient to answer using the words and the number (e.g. “none – unaware of coughing” and “0”).
- For patients discharged home during treatment, the site/study staff will ask the patient the questions by telephone/video link and the patient should have a copy of the BCSS questionnaire for reference whether they are hospitalised or discharged.
- This is a patient reported outcome, so for patients that are unable to complete the BCSS due to their medical condition i.e. if they are receiving ventilation, the reason for non-completion should be recorded in the source documents.
- The applicable score (number) for each question should be recorded in the source documents as well as the date, time and method of assessment.

## 6.8 Vital Signs

Vital signs include temperature, respiratory rate, heart rate and blood pressure should be recorded daily whilst the patient is hospitalised. Vital signs should be assessed at the same time as the daily physical examination. When the patient is discharged home vital sign assessments will not be recorded.

Blood pressure and pulse should be measured in the supine position and it is recommended that the patient should have rested quietly for at least 3 minutes prior to the measurement.

## 6.9 NEWS2

The data required for NEWS2 will be collected by the site staff and NEWS2 will be calculated by the Sponsor.

NEWS2 is a tool developed by the Royal College of Physicians, which improves the detection and response to clinical deterioration in adult patients and is a key element of patient safety and improving patient outcomes (12).

NEWS2 is based on a simple aggregate scoring system in which a score is allocated to physiological measurements, already recorded in routine practice, when patients present to, or are being monitored in hospital.

Six simple physiological parameters form the basis of the scoring system:

1. Respiration rate
2. Oxygen saturation
3. Any supplementary oxygen
4. Temperature
5. Systolic blood pressure
6. Heart rate
7. Alert, Voice, Pain, Unresponsive.

The highest NEWS2 score for each calendar day should be collected. The highest NEWS2 score will be recorded daily, for each calendar day, whilst the patient is hospitalised. When the patient is discharged home, NEWS2 will not be recorded.

### 6.10 Quality of Life Measured Using EQ-5D-5L

The EQ-5D-5L health-related quality of life questionnaire will be completed on Day 0, Day 7, Day 15, Day 28, Day 60 and Day 90 for all patients (see Appendix D).

In addition, the mobility, self-care and usual activities dimensions of the questionnaire will be assessed daily from Day 1 to Day 35.

The EQ-5D-5L provides a simple descriptive profile and a single index value for health status. The EQ-5D-5L self-rated questionnaire includes a visual analogue scale (VAS), which records the respondent's self-rated health status on a graduated (0–100) scale, with higher scores for higher health-related quality of life. It also includes the EQ-5D-5L descriptive system, which comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension. This questionnaire should only be completed if an approved translation in the language required by the patient is available. If an approved translation is not available, this assessment will not be conducted and will not be recorded as a protocol deviation.

### 6.11 COVID-19 symptom assessment

The presence of COVID-19 symptoms will be assessed as per the study schedule.

A checklist/worksheet will be provided to study site staff to document the COVID-19 symptoms. The questionnaire is provided in Appendix F.

### 6.12 Assessment of Long-COVID-19 symptoms

Assessment of long-COVID-19 symptoms will be performed on Day 15, Day 28, Day 60 and Day 90. The following patient reported outcome measures will be used:

- General Anxiety Disorder 7 Questionnaire (GAD-7)
- Patient Health Questionnaire-9 (PHQ-9)
- Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue Scale (Version 4)
- Brief Pain Inventory (Short Form)

The questionnaires are included in Appendix E and should only be completed if approved translations in the language(s) required by the patient(s) are available. If approved translations are not available, these assessments will not be conducted and will not be recorded as protocol deviations.

### 6.13 Samples for Laboratory Assessment

#### 6.13.1 Urine Pregnancy Test

Early detection pregnancy strips (minimum detection 10 MIU human chorionic gonadotrophin) will be used on Day 0.

Urine pregnancy testing is not required for women who are not of child-bearing potential. Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal.

Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age specific requirements apply:

- Women <50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and if FSH levels are in the postmenopausal range. If the FSH result is not available at the time of randomisation, the patient must have a negative pregnancy test and agree to use approved contraceptive method. The patient must have been using this contraceptive method for a period of 3 month prior to randomisation.
- Women ≥50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

### 6.13.2 Blood Sample for Immunogenicity Testing

A blood sample will be taken as per the study schedule for immunogenicity testing. This will be completed in all sites and for all patients, where collection of samples is feasible. If a site is not able to participate in immunogenicity sample collection, this will not preclude them from participation in the study. The sample will require processing to obtain serum which is required for the analysis and analysis testing will be completed using validated methods. A laboratory manual describing the requirements for the blood sample and the processing of the sample will be provided separately by the Sponsor (or delegate).

Immunogenicity will be determined by the presence of anti-drug antibodies (ADAs). A tiered analysis approach will be followed, whereby samples positive at the screening step will be confirmed for ADA presence. The confirmed positive samples will then be assessed for ADA titre and the presence of neutralising antibodies.

### 6.13.3 CCI

CCI

CCI

## 6.14 Concomitant Medications

Medications taken by the patient at the time of informed consent should be recorded in the source data. After this, patients will be asked at each visit if they have taken any new concomitant medications or changed any current medications. Alternatively, information can be obtained from the patient's hospital prescription record. The dosage information, dates of administration and reasons for use will be recorded.

Any other medications which are considered necessary for the patient's welfare should be given at the discretion of the Investigator.

Special care will be taken in questioning the patients on any possible self-medication.

SOC medications for the treatment of COVID-19 (e.g. remdesivir or dexamethasone) can be administered, as required. SOC should be recorded as concomitant medications.

Oxygen therapy will be recorded as concomitant medication.

## 6.15 Prohibited Medications

Interferons have been reported to reduce the activity of hepatic cytochrome P450 dependent enzymes in humans and animals. Caution should be exercised with patients who are taking medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance (e.g. some classes of antidepressants). Investigators are able to enrol these patients to the study but should be aware of the possible contraindication.

Patients who have received a prior SARS-CoV-2 vaccination may be enrolled into the study. However, patients enrolled into the study should be advised to refrain from receiving vaccinations, including SARS-CoV-2 vaccinations, during the treatment and follow-up phase up to Day 35, as these could interfere with study assessments.

### 6.16 Co-Enrolment into Additional Interventional Studies

Co-enrolment into other interventional studies during the treatment and follow-up phases up to Day 35 should be avoided, as it could interfere with study assessments. Co-enrolment into any study must be discussed with the Medical Monitor to clarify whether co-enrolment is permitted.

## 7 ADVERSE EVENT REPORTING

### 7.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical trial patient during the study; the event does not necessarily have a causal relationship with that treatment. An AE can therefore be any unfavourable and unintended sign (including any clinically significant abnormal laboratory finding), symptom or disease, temporally associated with the use of a medicinal product.

AEs may include the following:

- Apparently unrelated illnesses, including the worsening of a pre-existing illness.
- Injury or accidents.

Patients will be asked about AEs at every study visit. General, non-directed questioning will be used to elicit reports of AEs. If a patient is seen by a physician not involved with the study in relation to an AE, the Investigator should make every effort to contact the treating physician in a timely manner in order to obtain all information necessary to facilitate appropriate reporting of the event.

- The terms ‘COVID-19’or ‘SARS-CoV-2’ should not be recorded as an AE.
- Individual symptoms related to COVID-19/SARS-CoV-2 infection (e.g. fever, breathlessness, fatigue) present at study entry should not be reported as AEs.
- Worsening of symptoms related to COVID-19/SARS-CoV-2 infection should be reported as AEs if, in the investigators’ opinion, the symptoms are clinically significant or lead to treatment.
- New symptoms related to COVID-19/SARS-CoV-2 infection that start after the initiation of study treatment should be reported as AEs.

## 7.2 Treatment-Emergent Adverse Events

A treatment-emergent adverse event (TEAE) is an AE that is new in onset, or is a pre-existing condition that is aggravated in severity or frequency, and occurs after the administration of the first dose of study medication. TEAEs include any clinically significant change from baseline readings in any of the study assessments.

Any abnormal result from study assessments will be recorded as an AE, if they result in study withdrawal, are associated with accompanying symptoms, lead to treatment, lead to further diagnostic tests, or is considered by the Investigator to be of clinical significance. These should be recorded in the source documents.

## 7.3 Serious Adverse Event

An SAE, according to ICH GCP, is any AE that meets any of the following outcomes:

- Results in death.
- Is life-threatening (i.e. at immediate risk of death).
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Consists of a congenital anomaly or birth defect.

AEs that may not result in death, may not be life-threatening, or do not require hospitalisation may be considered SAEs when, based upon appropriate medical judgment, they may jeopardise the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. These events must be reported in the same manner as SAEs.

Deterioration of a patient's condition requiring admission to the intensive care unit or invasive mechanical ventilation, (whichever happens first) must be reported as an SAE.

Elective and pre-planned surgeries will not be reported as SAEs. Such procedures should be recorded as part of the medical history.

## 7.4 Assessment of Adverse Event

The Investigator will assess every AE to determine if it is serious or not (see Section 7.3 for definition criteria). This assessment will determine the reporting procedures to be followed.

### 7.4.1 Relationship to Study Medication

Investigators (or delegates) need to assess the causality and severity (intensity) between the study medication and/or concomitant medication and the AE; this information will be recorded in the source documents.

#### 7.4.1.1 Causality

Causality is the relationship between the study medication and the occurrence of the AE. Determination of causality is based on the Investigator's clinical judgment regarding the likelihood that the study medication caused the AE and may include consideration of some or all of the following factors:

- Alternative possible causes of the AE, including the patient's underlying disease or co-morbid conditions, other drugs, other host and environmental factors.
- The temporal sequence between the study medication exposure and the AE.
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or toxicity of the study medication.

Investigators need to assess the relationship of AEs to the study medication by consulting the IB and using the following definitions:

| | |
|---|---|
| **Definitely related**: | A causal relationship of the onset of the event relative to administration of the study medication and there is no other cause to explain the event. |
| **Probably related:** | A causal relationship is clinically/biologically reasonable relative to the administration of the study medication and the event is more likely explained by exposure to the study medication than by other factors or causes. |
| **Possibly related:** | A causal relationship is clinically/biologically reasonable relative to the administration of the study medication, but the event could have been due to another equally likely cause. |
| **Unlikely to be related:** | A causal relationship is considered unlikely to be related to use of the study medication if there are factors (evidence) explaining the occurrence of the event (e.g., progression of the underlying disease, concomitant medication more likely associated with the event) or a convincing alternative explanation for the event. |
| **Unrelated:** | A causal relationship is not reasonably related in time to the administration of the study medication, or exposure to the study medication has not occurred. |

#### 7.4.1.2 Severity

Severity (intensity) should be assessed according to the following definitions:

| | |
|---|---|
| **Mild:** | The patient is aware of the event or symptom, but the event or symptom is easily tolerated, causing minimal discomfort to the patient. The event or symptom should not interfere with everyday activities. |
| **Moderate:** | The patient experiences sufficient discomfort to interfere with or reduce normal everyday activities, but responds to symptomatic therapy or rest. |
| **Severe:** | Significant impairment of functioning: the patient is unable to carry out normal everyday activities despite symptomatic therapy and/or the patient's life is at risk from the AE. |

Note the distinction between the gravity and the severity (intensity) of an AE. Severe is a measure of intensity: thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for SAEs listed above.

### 7.5 Discontinuation of Study Medication Due to an AE

Study medication may be discontinued (temporarily or permanently) in response to an AE at any time at the discretion of the patient and/or the Investigator. This will be reported on the AE page in the eCRF.

The Sponsor (or delegate) will be informed as soon as possible of any patient for whom permanent discontinuation of study medication occurs.

### 7.6 Pregnancy

Pregnancy itself is not an AE unless there is a suspicion that the study medication may have interfered with the effectiveness of a contraceptive medication. However, if a female patient becomes pregnant during the conduct of the study, study medication will be discontinued immediately, and the Sponsor (or delegate) should be notified within 24 hours using the Pregnancy Report Form. Follow-up information regarding the outcome of the pregnancy and any foetal or neonatal sequelae should be obtained and documented. For all pregnant patients, on behalf of the Sponsor, study staff will discuss referral for specialist counselling on the possible risks to the unborn baby, and arrangements will be offered to monitor the health of both the patient and the unborn baby.

## 7.7 Adverse Events Recording and Reporting

### 7.7.1 Reporting of Adverse Events

All AEs and TEAEs will be reported from the day informed consent is obtained until 28 days after the last administration of the study medication. This includes AEs reported as a result of study procedures.

All AEs and TEAEs occurring during the study assessed by the Investigator (or delegate) as definitely, probably or possibly related to the study medication are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic or stable to the extent that they can be fully characterised (all follow-up results are to be reported to the sponsor or delegated Clinical Research Organisation [CRO] if requested).

### 7.7.2 Recording of Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical trials is crucial for the protection of patients, Investigators, and the Sponsor, and is mandated by regulatory agencies. The Sponsor (and delegated CRO) has established standard operating procedures (SOPs) in conformity with regulatory requirements to ensure appropriate reporting of safety information. The process for reporting AEs and SAEs at each site will be assessed by the Sponsor to ensure full compliance with the regulatory requirements.

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the trial patient using concise medical terminology.

All AEs and TEAEs, regardless of seriousness, severity, or causal relationship to study medication will be recorded in the source documents. The following items are to be included:

Description of event: whenever possible, signs and symptoms due to a common aetiology will be reported as an integrated diagnosis: e.g. cough, runny nose, sneezing, sore throat, and head congestion would be reported as “upper respiratory infection”. The diagnosis or description will be as specific and complete as possible (i.e. “lower extremity oedema”, rather than just “oedema”).

If a medical condition is known to have caused the injury or accident (e.g. a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as two separate AEs.

In cases of surgical or diagnostic procedures, the condition/illness leading to the procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as the SAE, and death is considered as its outcome.

## 7.8 Reporting of Serious Adverse Events

All AEs assessed as serious by the Investigator (or delegate) according to the criteria specified should be reported and recorded on a SAE form.

SAEs should be reported by the Investigator (or delegated person) to the Sponsor (or delegate), using the SAE report form provided, immediately (and not later than 24 hours) of a member of the site staff becoming aware of the event, whether or not the event is considered to be related to study medication. This initial report can be made by telephone or in writing. If the initial SAE report is made by telephone, a written report signed by the Investigator (or delegate) must be submitted immediately (and not later than 24 hours from the start of the event).

All SAEs will be reported from the day informed consent is obtained until 28 days after the last administration of the study medication. SAEs are to be followed until resolution regardless of whether the patient is still participating in the study.

Resolution means:

- The patient has returned to their baseline condition or the Investigator does not expect any further improvement or worsening of the event, or
- The SAE is deemed medically insignificant by the Investigator, or
- The SAE is resolved with residual effects.

**Details of the contact numbers for SAE reporting can be found in the Investigator's Site File.**

In addition to informing the Sponsor, the Investigator at the study site should notify the host organisation (e.g. Research and Development [R&D]) or any other department as required by local regulations if applicable.

The Sponsor will be responsible for informing the following within the stipulated reporting timelines:

- The Chief Investigator and site investigators
- Institutional Review Board/Independent Ethics Committee (IRB/IEC), and
- The appropriate local regulatory authority

The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Copies of all correspondence relating to the reporting of SAEs should be maintained in the Investigator Site File and provided to the Sponsor (or delegate). The Investigator will be informed by the Sponsor (or delegate) of any SAEs from other Investigators or clinical studies which have safety implications.

# 8 DATA ANALYSIS/STATISTICAL METHODS

Data will be entered into a database. The Sponsor (or delegate) will be responsible for data processing and analysis, in accordance with the appropriate data management and analysis procedures.

Analysis methods for key endpoints are described below. Further details on all analyses will be described in the Statistical Analysis Plan (SAP).

## 8.1 Sample Size Determination

Success will be determined if at least one of the primary endpoints is declared statistically significant by the primary analysis. A sample size of 610 patients in total using a 1:1 randomisation ratio (305 patients 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 also allows for an interim analysis to assess futility after the first 300 randomised patients have completed the Day 35 visit or have withdrawn from the study.

The sample size calculation assumes a hospital discharge rate in the placebo treatment arm of 70% at Day 28, a recovery rate in the placebo treatment arm of 30% at Day 28 and a dropout rate of 25% over the 28-day evaluation period with time to dropout exponentially distributed.

By their definition the two primary endpoints are naturally correlated. This correlation has been estimated from prior study data and has also been considered in the sample size calculation.

More details regarding the sample size calculation used for the study will be provided in the SAP.

The key secondary endpoint of progression to severe disease or death within the 35-day study period will be formally tested, provided statistical significance is declared in both of the primary endpoints.

## 8.2 Randomisation

This is a double-blind study. Patients will be randomised to one of two treatment groups (SNG001 or placebo). The randomisation will be stratified by site. A pre-specified randomisation schedule will be generated using a 1:1 randomisation ratio.

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

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

## 8.3 Analysis Populations

The intention-to-treat (ITT) population is defined as all randomised patients.

The safety population will include all randomised patients who receive at least one dose of study drug. Patients will be analysed as treated and not per randomised treatment.

The per protocol population will include all patients in the ITT population who do not have any protocol deviations with an impact on efficacy on or prior to Day 35.

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## 8.4 Estimands and Intercurrent Events

### 8.4.1 Primary Efficacy Estimands

The first 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 follows:

| **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 | Treatment policy: The time to hospital discharge will be used regardless of study withdrawal and regardless of the duration of follow-up following hospital discharge. This assumes relapse is independent to the treatment effect. |
| 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. |

A tipping point analysis will be performed to implement a treatment policy strategy for patients who withdraw from the study prior to hospital discharge and prior to Day 28 by imputing missing discharge times. The imputation will be repeated by adjusting the likelihood of hospital discharge in each treatment arm independently, to varying degrees. The first primary analysis will be performed on each of the imputed datasets to test the sensitivity to missing data.

A further sensitivity analysis of the first primary estimand will test the missing at random assumption by imputing missing data after study withdrawal through a missing not at random approach.

A supportive analysis will estimate the hazard ratio of SNG001 versus placebo for the time to hospital discharge of patients in the per protocol population. Intercurrent events will be handled as follows:

| **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. 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. |
| Other premature treatment discontinuation | Treatment policy: The time to hospital discharge will be used regardless of treatment discontinuation. |
| Withdrawal from study following hospital discharge | Treatment policy: The time to hospital discharge will be used regardless of study withdrawal and regardless of the duration of follow-up following hospital discharge. This assumes relapse is independent to the treatment effect. |
| 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 concomitant | Hypothetical (estimand for a situation with no protocol deviations or concomitant medications affecting efficacy): To establish the true treatment effect the time to hospital discharge will be considered missing if protocol deviations |

| Intercurrent event | Policy |
|---|---|
| medications affecting efficacy | or medications affecting efficacy are recorded on or prior to Day 35. |

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 follows:

| 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 | Treatment policy: The time to recovery will be used regardless of study withdrawal and regardless of the duration of follow-up following recovery. This assumes relapse is independent to the treatment effect. |
| 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. |

A tipping point analysis will be performed to implement a treatment policy strategy for patients who withdraw from the study prior to recovery and prior to Day 28 by imputing missing recovery times. The imputation will be repeated by adjusting the likelihood of recovery in each treatment arm independently, to varying degrees. The second primary analysis will be performed on each of the imputed datasets to test the sensitivity to missing data.

A further sensitivity analysis of the second primary estimand will test the missing at random assumption by imputing missing data after study withdrawal through a missing not at random approach.

A supportive analysis will estimate the hazard ratio of SNG001 versus placebo for the time to recovery of patients in the per protocol population. Intercurrent events will be handled as follows:

| **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. 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. |
| Other premature treatment discontinuation | Treatment policy: The time to recovery will be used regardless of treatment discontinuation. |
| Withdrawal from study following recovery | Treatment policy: The time to recovery will be used regardless of study withdrawal and regardless of the duration of follow-up following recovery. This assumes relapse is independent to the treatment effect. |
| 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 concomitant medications affecting efficacy | Hypothetical (estimand for a situation with no deviations or concomitant medication affecting efficacy): To establish the true treatment effect the time to recovery will be considered missing if protocol deviations or medications affecting efficacy are recorded on or prior to Day 35. |

### 8.4.2 Key Secondary Efficacy Estimands

The first 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 (or randomisation date if the patient is not dosed) of patients in the ITT population. Intercurrent events will be handled as follows:

| Intercurrent event | Policy |
|---|---|
| Death | Composite variable: The definition of severe disease includes patients who die within 35 days of first dose (or randomisation date if the patient is not dosed), regardless of their WHO 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. |

A tipping point analysis will be performed to implement a treatment policy strategy for patients who withdraw from the study prior to progressing to severe disease and prior to Day 35 by imputing severe disease for patients with missing data. The imputation will be repeated by adjusting the probability of severe disease in each treatment arm independently and recalculating the differences in proportions for each imputed dataset.

A further sensitivity analysis will test the missing at random assumption by imputing severe disease for patients with missing data through a missing not at random approach. Sensitivity analyses will also be conducted only including patients who completed Day 28 and only including patients who withdrew from the study prior to Day 35.

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 (or randomisation date if the patient is not dosed) will be estimated for the per protocol population. Intercurrent events will be handled as follows:

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

| Intercurrent event | Policy |
|---|---|
| | therefore this approach will help establish the true treatment effect. |
| Other premature treatment discontinuation | Treatment policy: Severe disease will be determined regardless of treatment discontinuation. |
| 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 | Hypothetical (estimand for a situation with no protocol deviations or concomitant medications affecting efficacy): To establish the true treatment effect all WHO OSCI assessments will be considered missing if protocol deviations or medications affecting efficacy are recorded on or prior to Day 35. |

The second 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 (or randomisation date if the patient is not dosed) of patients in the ITT population. The third key secondary estimand will be the difference in probabilities for SNG001 versus placebo for death within 35 days of first dose (or randomisation date if the patient is not dosed) of patients in the ITT population. For both the second and third key secondary endpoints the same policies will be used for handling intercurrent events as progression to severe disease or death.

## 8.5 Statistical Analysis Methodology for Efficacy Endpoints

A SAP will be completed prior to study unblinding and database lock.

All collected data will be summarized using descriptive statistics. Summary statistics will consist of the number of observations, mean, standard deviation, minimum, median, and maximum for continuous parameters, and number and percent of subjects for categorical parameters. Changes respective to Baseline will also be evaluated where applicable. Baseline is defined as the last assessment prior to first dose.

### 8.5.1 Analysis of the Primary Efficacy Endpoint

The same method of analysis will be used for both primary endpoints. The primary analysis will use a Cox proportional hazards model. Time to hospital discharge and time to recovery will be determined using data collected up to Day 28 only. WHO OSCI data collected after Day 28 will only be used to assess relapse for patients who were discharged or recovered prior to Day 28. Relapse will be defined as a WHO OSCI score of >2 for hospital discharge and a WHO OSCI score of >1 for recovery. Patients who die will be administratively censored at Day 28, i.e. time to hospital discharge and time to recovery will be fixed at 28 days for these patients. Patients who neither recover nor die will be censored at the date of their last WHO OSCI assessment where discharge/recovery was not possible. Covariates will be included for treatment arm, age (as a continuous variable), sex, and Country/Region. Further covariates

may be defined in the SAP. The hazard ratio for recovery of SNG001 versus placebo, 95% confidence intervals (CI) and p-value will be presented.

Ties in event times will be handled using the exact method, or the Efron approximation if computational difficulties arise.

In addition, Kaplan-Meier estimates of time to hospital discharge and time to recovery for 25%, 50% (median time) and 75% of patients will be presented.

### 8.5.2 Analysis of the Key Secondary Efficacy Endpoints

For the first key secondary endpoint of progression to severe disease or death, a logistic regression model will be applied. The difference in the probability of severe disease progression between SNG001 and placebo will be presented alongside the 95% CIs and p-values. The covariates used for the primary analysis will also be used for the key secondary analysis.

Progression to intubation or death and death will be analysed using the same methods described for the first key secondary endpoint, provided enough events are observed to make the analysis possible.

### 8.5.3 Analysis of Secondary Efficacy Endpoints

All analyses of secondary endpoints described below will include the covariates used for the primary analysis, unless stated otherwise.

Recovery and hospital discharge will be analysed at Days 7, 14, 21 and 28 using a logistic regression model to determine the difference in proportions for SNG001 versus placebo.

Improvement on the WHO OSCI scale will be analysed at Days 7, 14, 21 and 28 assessed using an ordered logistic regression model assuming proportional odds to estimate the odds ratios for SNG001 versus placebo. Adjacent WHO OSCI categories may be merged for some or all visits if the outcome frequency for some WHO OSCI levels is low for any treatment arm.

Observed WHO OSCI scores will also be summarised descriptively.

Change from baseline in breathlessness and cough scores according to the BCSS and total BCSS score will be assessed using a mixed model for repeated measures. The difference between SNG001 and Placebo across the treatment period (up to Day 14) will be estimated alongside the 95% CIs and p-values. The covariates used for the primary analysis will be used with an additional covariate for baseline score.

### 8.5.4 Multiple Testing Strategy

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.

### 8.5.5 Handling of Missing Data

For analyses using the WHO OSCI, including the primary and key secondary endpoints, patients with a WHO OSCI score of 8, indicating death, will have any subsequent missing WHO OSCI assessments imputed as 8. In addition, if other data sources such as AEs indicate a patient has died all missing WHO OSCI scores on and after the date of death will be imputed as 8.

For relevant analyses, missing WHO OSCI assessments for patients who withdraw from the study alive will be imputed using multiple imputation under a missing at random assumption. Selected analyses will be repeated using a missing not at random approach through an imputation model estimated from patients in the placebo group.

For the mixed models with repeated measures (MMRM) of breathlessness, missing breathlessness scores will be imputed as 4 if the WHO OSCI score at the corresponding visit is ≥5. Cough and sputum scores at corresponding visits will be considered missing at random and total BCSS scores will be calculated by summing the imputed symptom scores, where possible. Missing breathlessness, cough and sputum scores at all other visits will be considered missing at random and will not explicitly be imputed but will be accounted for by the MMRM analysis. Missing not at random approaches may also be considered for sensitivity analyses.

Further details regarding missing data approaches will be given in the SAP.

## 8.6 Safety Analysis

Safety analyses will be based primarily on AE/SAE information which will be summarised descriptively, including a summary of treatment-emergent AEs/SAEs. AEs/SAEs will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. Summaries by severity and drug-relatedness will also be presented. All SAEs and SUSARs will be summarised according to seriousness categorisation, number, event preferred term, duration of treatment prior to event, rechallenge information and outcomes.

Vital signs will be summarised by time point for each treatment group and overall.

Immunogenicity will be summarised by presentation of the number and percentage of patients with ADAs at each timepoint and overall. Descriptive statistics of ADA titres may be summarised if sufficient data are available.

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## 8.8 Other Analyses

Tabulations will be provided for completion/withdrawal status, protocol deviations, study populations, demographic and other baseline characteristics, use of concomitant medications, and exposure of and compliance with study drug.

## 8.9 Subgroup Analyses

The following subgroups will be considered for analysis, other subgroups may be defined in the SAP:

- Age category
- Presence of comorbidities
- Current smoking status
- Sex
- Race
- Prior duration of symptoms
- BMI

The details of analyses to be performed for the subgroups will be defined in the SAP.

## 8.10 Interim Analyses

An unblinded interim analysis will be conducted by an independent team 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. If feasible, it is planned to assess futility on the first 300 randomised patients once all of these patients have completed the Day 35 visit or have withdrawn from the study. The primary analyses for the two primary endpoints will be conducted for the interim analysis and provided to an IDMC which may include some or all members of the DSMC. The go/no go recommendation made by an IDMC will be based on a non-binding criterion described in the table below.

| Criterion | Recommendation |
|---|---|
| 1. the Z statistic from the estimate of treatment effect from the analysis for time to discharge is less than 1.4 *and* | Stop the study for futility |

| | |
|---|---|
| 2. the Z statistic from the estimate of treatment effect from the analysis for time to recovery is less than 1.4 | |
| Otherwise | Continue the study so that at least 610 patients in total are randomised. |

In addition, summaries and appropriate analyses of death, intubation or death and severe disease or death will be supplied to the IDMC and should be considered in their recommendation. Full details will be provided in an IDMC charter.

### 8.11 Primary Analysis

A primary analysis will take place once all randomised patients have completed their Day 35 visit or have withdrawn from the study. The primary analysis will be used to assess the study data against the study objectives. All data summaries documented in the SAP will be produced for the primary analysis and will be reported in a CSR, with the exception of any Day 90 summaries. The study will be fully unblinded at an aggregate level. Specific team members will be unblinded at an individual level, as required for decision making. Full details will be provided in the study unblinding plan. A follow-up analysis will be conducted once all patients have completed the Day 90 visit or have withdrawn from the study.

### 8.12 Independent Data Monitoring Committee/Data Safety Monitoring Committee

The IDMC/DSMC is an independent multidisciplinary group consisting of suitably qualified individuals who, collectively, have experience in the management of patients with infectious disease (e.g. respiratory viral infections), clinical pharmacology, and/or pharmacovigilance, and in the conduct and oversight of randomised clinical trials.

The DSMC will be responsible for safeguarding the interests of trial patients, assessing the safety of the interventions during the study and for making recommendations about the progress of the study. This will include providing recommendations about necessary changes to the study protocol and/or whether to stop or continue the study.

The DSMC will be advisory to the Chief Investigator, the study team and any other Sponsor representative. The Chief Investigator and Sponsor will be responsible for promptly reviewing the DSMC recommendations, to decide whether to continue, extend or terminate the trial. In addition, the DSMC will advise the Chief Investigator and the Sponsor whether measurements are to be repeated by patients, amendments to the protocol are to be made, or changes in study conduct are required.

The DSMC will also (acting as the IDMC) assess the need for and feasibility of an unblinded interim analysis as described in Section 8.10. The IDMC/DSMC will be guided by the IDMC/DSMC Charter. The Charter will define the primary responsibilities of the IDMC/DSMC, its membership and the purpose and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and proper communication and outline the contents of the reports that will be provided to the IDMC/DSMC.

# 9 QUALITY CONTROL AND QUALITY ASSURANCE

## 9.1 Quality Control (Monitoring)

In order to verify that the study is conducted in accordance with the study protocol, ICH GCP, local regulatory requirements and other applicable guidelines, data will be monitored at regular intervals. This will allow the sponsor to ensure that the data is authentic, accurate and complete. Source data will be verified either on site or remotely. If remote source data verification is required, due to its limitations, critical data such as primary efficacy data and important safety data will be its focus and will comply with local and national regulations. The study Monitoring Plan provides further details on specific monitoring activities.

## 9.2 Quality Assurance

The Sponsor or its designated representative will assess each study site to verify the qualifications of each Investigator and the site staff and to ensure that the site has all of the required equipment. An Investigators Meeting and/or Site Initiation Meeting will occur where among other things the Investigator will be informed of their responsibilities and procedures for ensuring adequate and correct study documentation.

The Investigator is required to complete the source documents designed to record all observations and other data pertinent to the study for each patient. Study data for each patient that gives informed consent for the study will be entered into the source documents by study site personnel.

Instances of missing, discrepant, or uninterpretable data will be queried with the Investigator for resolution. Any changes to study data will be made to the source documents and documented in an audit trail, which will be maintained within the clinical database.

In compliance with ICH GCP and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies, IRBs or IECs may conduct quality assurance audits at any time during or following a study. The Investigator must agree to allow regular monitoring of the study according to ICH GCP requirements and other guidelines and local regulations. The Investigator should also agree to allow auditors direct access to all study-related documents including source documents. They must also agree to allocate their time and the time of their study staff to the auditors in order to discuss findings and issues.

# 10 DATA HANDLING AND RECORD KEEPING

## 10.1 Source Documents and Electronic Case Report Form

The Investigator and their study team will be responsible for entering data into the source documents. The Principal Investigator is responsible for ensuring the accuracy of the data entered. The source documents should be completed during the study visit and once completed, site staff should enter the data into the eCRF.

It is possible that source data may be captured in different locations, for example, patient medical records or directly onto other source documents.

If permitted by local regulations, study worksheets can be provided as a tool for sites to ensure complete collection of source data and to support the sites in correct collection of COVID-19 key symptoms, COVID-19 history data**,** physical examination and PK time point information. If used, the worksheets will comply with any local regulations, ICH GCP principles and will follow ALCOA standards to achieve data quality. The process for recording source data will be documented at site level and more general information included in the monitoring plan.

For screen failures, source documents will not be monitored. The patient's unique identification number, date of screening, date of informed consent and reason for screen failure should be entered into the eCRF. Please note, no other data need be entered into the eCRF for screen failures.

### 10.2 Record Retention

Essential documents as defined by ICH GCP are not limited to, but include, all signed protocols and any amendment(s), copies of the completed source documents, signed informed consent forms/other records of informed consent from all patients who consented, hospital records, diary cards and other source documents, R&D and IEC approvals, copies of previous versions of all study documentation and all related correspondence including approved documents, drug accountability records, study correspondence and a list of the patients' names and addresses.

The Investigator and/or Sponsor must retain copies of the essential documents for a minimum of 25 years following the end of the study.

The Investigator will inform the Sponsor of the storage location of the essential documents and of any changes in the storage location should they occur. The Investigator must contact the Sponsor for approval before disposing of any documentation. The Investigator should take measures to prevent accidental or premature destruction of these documents.

## 11 REGULATORY AND ETHICS

### 11.1 Regulatory and Ethics Considerations

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations.

Procedures to be followed will be those documented in the protocol, study site or Sponsor (or delegate's) SOPs, manuals and guidelines.

### 11.2 Competent Authority Approval

Before the study is initiated at a site, the Sponsor will obtain approval to conduct the study from the Competent Authority in each of the countries in which this study will be performed (e.g. Medicines and Healthcare products Regulatory Agency [MHRA] in the UK).

## 11.3 Institutional Review Board/Independent Ethics Committee and Hospital Board Requirements

The Sponsor is responsible for ensuring IRB/IEC approval of the study. Approval of the protocol, informed consent form, advertising and any other information presented to, or seen by, potential patients must be obtained from the appropriate IRB/IEC before the study starts. If a substantial amendment is required during the study, IRB/IEC approval must be obtained prior to their implementation. The Principal Investigators are responsible for ensuring that these actions occur.

If appropriate, as well as approval by the IRB/IEC, prior to starting, the study should obtain approval from the site Hospital Board or other relevant body (e.g. R&D department). Once written approval has been obtained from the country's competent authority (e.g. MHRA), the IRB/IEC, and the site's relevant hospital body, and all other necessary documentation has been received, the Sponsor (or delegate) will release the study drug and patient recruitment can commence.

Similarly, the Investigator/Chief Investigator must inform the relevant hospital body of all substantial amendments and forward to them evidence of IRB/IEC and competent authority (if appropriate) approval. Amendment approval should be received from the relevant hospital body prior to implementation at site.

## 11.4 Informed Consent and Screening Data

Patient informed consent forms will be provided by the Sponsor and will be approved by the IRB/REC. Any changes requested by the IRB/IEC must be approved by the Sponsor (or delegate) prior to the documents being used.

Informed consent will be obtained from each patient prior to any study procedures being performed and data reported.

## 11.5 Patient Confidentiality

The Investigator must ensure that the patients' anonymity is maintained. On the source documents and any other documents submitted to the Sponsor, patients should NOT be identified by their names, but by the assigned unique patient identification number only.

The Investigator (or delegate) should keep a confidential log of the names of all patients and the patient numbers that they have been allocated in order to be able to reveal the identity of the patient should this be required for safety purposes. Documents not for submission to the Sponsor (e.g. signed informed consent forms) should be maintained by the Investigator in strict confidence.

## 11.6 Investigator Compliance

The Investigator must be familiar with the study protocol, the IB, the conduct of the study and also their responsibilities as an Investigator according to the ICH GCP guidelines.

No modifications to the protocol will be made without the approval of both the Chief Investigator and the Sponsor. Changes that significantly affect the safety of the patients, the scope of the investigation, or the scientific quality of the study (i.e. efficacy assessments) will require IRB/IEC and regulatory authority (where required) notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human patients.

When circumstances require an immediate departure from procedures set forth in the protocol, the Investigator will contact the Sponsor to discuss the planned course of action. If possible, contact will be made before the implementation of any changes. Any departures from protocol will be fully documented in the source documentation and in the eCRF and/or a protocol deviation log.

### 11.7 Progress Reports and Safety Reports

Progress and Safety reports should be submitted to the IRB/IEC, competent authority and any necessary local site department as per the country specific requirements. It is the Sponsors responsibility to ensure this happens.

## 12 DEFINITION OF END OF TRIAL

End of Trial is defined as: Last Patient, Last Visit.

## 13 SPONSOR DISCONTINUATION CRITERIA

### 13.1 Study Sites

The Sponsor has the authority to stop activity at any individual site at any time during the study.

### 13.2 Entire Study

The study will be terminated early if, in the opinion of the Sponsor or Chief Investigator, an unacceptable risk to the safety and welfare of patients is posed by the continuation of the study in light of the data generated. Premature termination of this study may also occur because of a regulatory authority decision, or a change in opinion of the IRB/IEC, or on the advice of the DSMC.

If suspension or termination of the study is necessary, the Sponsor will endeavour to provide advance notification to the sites. The Sponsor should promptly inform each Investigator of its decision and then the Investigator (or delegate) should promptly inform the institution (where applicable) and also the IRB/IEC and any necessary local site department, providing them with a detailed written explanation of the termination or suspension. The Investigator (or delegate) should also promptly inform the trial patients and should assure appropriate therapy and follow up for the patients. In such cases, all study data and unused study medication must be returned to the Sponsor.

# 14 PUBLICATION OF STUDY RESULTS

The Sponsor commits to publish the results of this study in a peer-reviewed journal of its choice. The results may also be published in a poster or oral presentation at one or more scientific meetings, conferences or symposia.

A clinical study report, written in accordance with the ICH E3 Guideline, will be submitted in accordance with local regulations.

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol, or elsewhere, will be considered the confidential and proprietary property of the Sponsor.

The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to the Investigator's employees and staff who have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of SNG001 and other drugs and diagnostics, and, therefore, may be disclosed as required to other Clinical Investigators, business partners and associates and government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between the Sponsor and the Investigator and/or the Investigator's institution.

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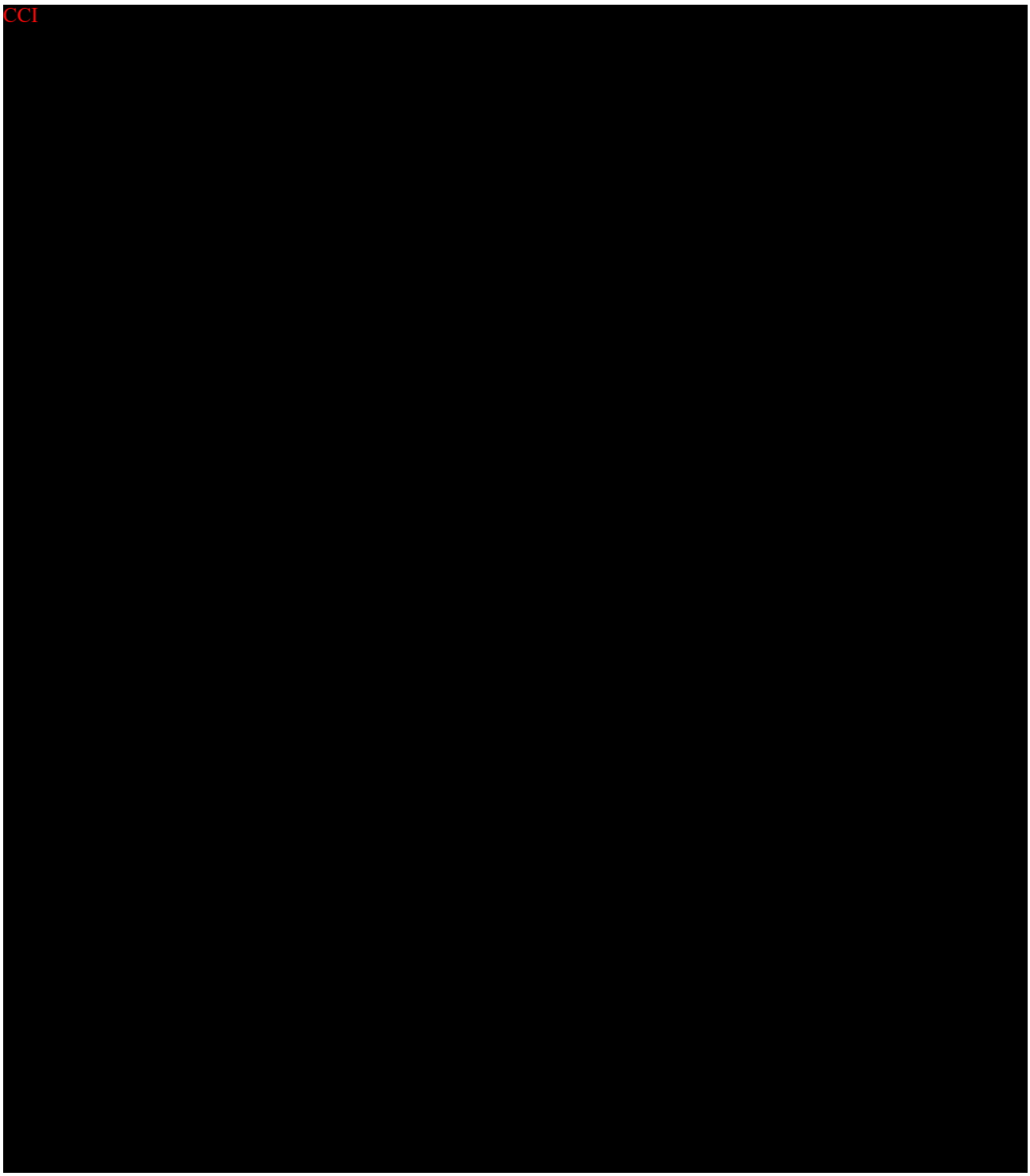

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# 16 REFERENCES

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