THE LANCET
Respiratory Medicine

Supplementary appendix

This appendix formed part of the original submission. We post it as supplied by the authors.

Supplement to: Monk P D, Marsden R J, Tear V J, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2020; published online November 12. http://dx.doi.org/10.1016/S2213-2600(20)30511-7.

SUPPLEMENTARY APPENDIX

Supplement to Monk PD, Marsden R, Tear VJ *et al*. *Safety and efficacy of inhaled SNG001 (IFN-β1a for nebulisation) for the treatment of patients with confirmed SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled trial.*

TABLE OF CONTENTS

1. STUDY GROUP

AFFILIATION	TITLE, NAME AND HIGHEST DEGREE
Institute for Clinical and Applied Health Research, Hull York Medical School, University of Hull, Hull, UK and Academic Respiratory Medicine, Hull University Teaching Hospitals NHS Trust, Castle Hill Hospital, Cottingham, UK	Dr MG Crooks MD
Department of Respiratory Medicine, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, UK and Institute of Inflammation and Ageing, University of Birmingham, Edgbaston, Birmingham, UK	Dr DPS Dosanjh DPhil
College of Life Sciences, NIHR Biomedical Research Centre (Respiratory Theme), Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK	Prof S Siddiqui FRCP
Oxford Respiratory Trials Unit, Oxford NIHR Biomedical Research Centre, University of Oxford	Prof NM Rahman DPhil
NIHR Manchester Biomedical Research Centre, The University of Manchester, Manchester, UK and NIHR Manchester Clinical Research Facility, Manchester University NHS Foundation Trust, Manchester, UK	Prof JA Smith PhD Dr A Horsley PhD
Nottingham NIHR Respiratory BRC, University of Nottingham, Nottingham, UK	Prof TW Harrison MD
NIHR National Patient Recruitment Centre, Bradford Institute for Health Research, Bradford, UK	Dr D Saralaya FRCP
Queen University Belfast, Wellcome-Wolfson Institute for Experimental Medicine, Northern Ireland, UK	Prof L McGarvey MD
NIHR Southampton Biomedical Research Centre, South Academic Block, University Hospital Southampton, Southampton UK and Clinical and Experimental Sciences, Medical Faculty, University of Southampton, Sir Henry Wellcome Laboratories, University Hospital Southampton, UK	Dr A Watson PhD
Data Magik Ltd, Laburnum House, East Grimstead, Salisbury, UK	Mr E Foster BA Mr A Fleet MSc
The Institute of Clinical Research, Grove Park Business Estate, Maidenhead, UK	Mrs S Hemmings BSc (Hons)
Medicines Evaluation Unit, Langley Building, Manchester University NHS Foundations Trust Hospital, Manchester, UK and Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, The University of Manchester, Manchester, UK	Prof D Singh MD
Synairgen Research Ltd, Southampton General Hospital, Southampton UK	Mrs S Aitken BA Dr S Dudley PhD Mrs R Beegan BSc Mrs A Thompson BA (Hons)
Synairgen Research Ltd, Southampton General Hospital, Southampton UK and University of Southampton, Southampton UK	Mr PMB Rodrigues MRes

2. METHODS

2.1. Selection of Study Population

2.1.1. Inclusion Criteria for Hospitalised Patients

Patient must fulfil the following criteria to be eligible for study entry:

1. Positive virus test for SARS-CoV-2 using reverse transcription-polymerase chain reaction (RT-PCR), or positive point-of-care viral infection test in the presence of strong clinical suspicion of SARS-CoV-2 infection.
2. Male or female, ≥18 years of age at the time of consent.

3. Admitted to hospital due to the severity of their COVID-19 disease who presented with clinical symptoms consistent with COVID-19:
    - High temperature and/or
    - New, continuous cough.
    - Loss or change to sense of smell and/or taste
4. Provided informed consent.
5. Hospitalised female patients had to be ≥1 year postmenopausal, surgically sterile, or using an acceptable method of contraception. Acceptable birth control methods were tubal occlusion, intrauterine device (provided coils were 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, intravaginal device (e.g., ethinylestradiol and etonogestrel), desogestrel (e.g., Cerazette™), total sexual abstinence and vasectomised sexual partner. Women had to be stable on their chosen method of birth control for a minimum of 3 months before entering the trial and had to continue with birth control for 1 month after the last dose of inhaled IFN-β1a/matching placebo. In addition to the acceptable birth control method (except for the practice of total sexual abstinence), condom (in UK with spermicides) had to 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.

    Women not of childbearing potential were defined as women who were either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who were postmenopausal. Women were considered postmenopausal if they had been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements applied:

    - Women <50 years old were considered postmenopausal if they had been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and if the follicle-stimulating hormone (FSH) levels were in the postmenopausal range.
    - Women ≥50 years old were considered postmenopausal if they had 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 was not possible, the decision to enrol a woman of childbearing potential had to be based on the benefit-risk for the patient, which had to be discussed with the patient at the time of the informed consent.

2.1.2. Exclusion Criteria for Hospitalised Patients

A patient was not eligible for inclusion in the study if any of the following criteria were met:

1. Any condition, including findings in the patients' medical history or in the pre-randomisation study assessments that in the opinion of the Investigator, constituted a risk or a contraindication for the participation of the patient into the study or that could have interfered with the study objectives, conduct or evaluation.
2. Current or previous participation in another clinical trial where the patient had received a dose of an Investigational Medicinal Product (IMP) containing small molecules within 30 days or 5 half-lives (whichever was longer) prior to entry into this study or containing biologicals within 3 months prior to entry into this study.
3. Ventilated or in intensive care.
4. Inability to use a nebuliser with a mouthpiece.
5. History of hypersensitivity to natural or recombinant IFN-β or to any of the excipients in the drug preparation.
6. Females who were breast-feeding, lactating, pregnant or intending to become pregnant.

2.2. Randomisation and Masking

Unique identification number

The unique patient identification number consisted of nine digits (two for the study number, three for the country [if applicable] and site number and four for patient number) and identified the patient throughout the study. The 4-digit patient number was assigned sequentially to each patient within each site starting with 1001 and was not re-assigned.

Patients were randomised to one of two treatment groups (SNG001 or placebo) in a 1:1 ratio according to a pre-specified randomisation schedule in addition to standard of care.

2.3. Description of Investigational Medicinal Product and Device

2.3.1. SNG001

SNG001 is an inhaled formulation of IFN-β1a, which was developed to treat viral exacerbations of asthma and chronic obstructive pulmonary disease (COPD).

The drug substance, recombinant IFN-β1a, was manufactured by Rentschler Biotechnologie GmbH (Laupheim, Germany). The drug product was manufactured by Vetter Development Services USA Inc (Illinois, USA).The drug product contained IFN-β1a and the excipients (trisodium citrate dihydrate, di-sodium hydrogen-phosphate, sodium dihydrogen-phosphate dihydrate, DL-methionine and water). Both drug substance and the drug product were manufactured under Good Manufacturing Practice (GMP) conditions.

The drug product was a sterile, clear and colourless, ready-to-use aqueous nebuliser solution (0.65 mL containing 12 MIU/mL IFN-β1a) presented in a disposable glass syringe and was stored at 5±3°C.

2.3.2. Placebo

Placebo contained all the excipients present in SNG001 with the exception of IFN-β1a. Placebo was presented in the identical syringes as the drug product.

2.3.3. Inhalation Devices

The study medication was delivered using the I-neb nebuliser. The I-neb (Philips Respironics) is a portable mesh nebuliser with adaptive aerosol delivery technology. The device was used in its tidal breathing mode (TBM). In TBM, the I-neb delivers short pulses of aerosol into each inhalation and requires the patient to use tidal breathing. The I-neb was used with a metering chamber that results in a 0.5 mL (6 MIU IFN-β1a) dose.

3. RESULTS

Table E1: Improvement from baseline on the OSCI scale (Intent-To-Treat)

	Placebo (N=50)	SNG001 (N=48)
Day 15/16		
Any improvement from baseline	35 (70.0%)	36 (75.0%)
Improvement of 1 OSCI level	11 (22.0%)	3 (6.3%)
Improvement of 2 OSCI levels	17 (34.0%)	16 (33.3%)
Improvement of 3 OSCI levels	6 (12.0%)	15 (31.3%)
Improvement of 4 or more OSCI levels	1 (2.0%)	2 (4.2%)
No improvement	15 (30.0%)	12 (25.0%)
Day 28		
Any improvement from baseline	37 (74.0%)	41 (85.4%)
Improvement of 1 OSCI level	8 (16.0%)	5 (10.4%)
Improvement of 2 OSCI levels	18 (36.0%)	11 (22.9%)
Improvement of 3 OSCI levels	8 (16.0%)	17 (35.4%)
Improvement of 4 or more OSCI levels	3 (6.0%)	8 (16.7%)
No improvement	13 (26.0%)	7 (14.6%)

Percentages are calculated using the total number of patients in each treatment group (N).
Any improvement is defined as a decrease from baseline in the OSCI at the corresponding visit.

Table E2: Recovery (Intent-To-Treat)

	Placebo (N=50)	SNG001 (N=48)
Day 15/16		
Recovered	11 (22.4%)	21 (43.8%)
Not-recovered	38 (77.6%)	27 (56.3%)
Day 28		
Recovered	17 (34.7%)	28 (58.3%)
Not-recovered	32 (65.3%)	20 (41.7%)

Recovered was defined as a post baseline OSCI score of 0 or 1 which does not rise above 1 at any subsequent visit.
Percentages were calculated using the total number of patients in each treatment group with OSCI at baseline >1.

Table E3: Discharge from Hospital (Intent-To-Treat)

	Placebo (N=50)	SNG001 (N=48)
Day 15/16		
Patients discharged from hospital	33 (68.8%)	35 (75.0%)
Patients not discharged from hospital	15 (31.5%)	13 (6.3%)
Day 28		
Patients discharged from hospital	36 (75.0%)	39 (81.3%)
Patients not discharged from hospital	12 (25.0%)	9 (18.8%)

Hospital discharge was defined as a post baseline OSCI score of 2 or less which does not rise above 2 at any subsequent visits.
Percentages were calculated using the total number of patients in each treatment group with OSCI at baseline >2.

Table E4 Summary of Treatment Emergent Adverse Events Reported in ≥2 Patients in Each Treatment Group by System Organ Class and Preferred Term

System Organ Class Preferred Term	Placebo (N=50)	SNG001 (N=48)
Nervous system disorders		
Headache	5 (10·0%)	7 (14·6%)
Dizziness	2 (4·0%)	2 (4·2%)
Respiratory, thoracic and mediastinal disorders		
Respiratory failure	6 (12·0%)	4 (8·4%)
Cough	1 (2·0%)	2 (4·2%)
Dyspnoea	2 (4·0%)	0
Gastrointestinal disorders		
Nausea	6 (12·0%)	1 (2·1%)
Constipation	2 (4·0%)	2 (4·2%)
Dyspepsia	0	2 (4·2%)
Infections and infestations		
COVID-19 pneumonia	3 (6·0%)	3 (6·3%)
Metabolism and nutrition disorders		
Hypokalaemia	3 (6·0%)	3 (6·3%)
Hypophosphataemia	3 (6·0%)	1 (2·1%)
Vascular disorders		
Hypertension	4 (8·0%)	0
Hypotension	0	2 (4·2%)
General disorders and administration site conditions		
Chest pain	2 (4·0%)	1 (2·1%)
Pyrexia	2 (4·0%)	0
Renal and urinary disorders		
Acute kidney injury	3 (6·0%)	1 (2·1%)
Psychiatric disorders		
Delirium	2 (4·0%)	1 (2·1%)

n = number of subjects with TEAEs. TEAE= treatment-emergent adverse event.

A TEAE was defined as an adverse event with onset date and time on or after the date and time of the first dose of study treatment.

Adverse events were coded using MedDRA version 23.

PROTOCOL

A randomised, double-blind, placebo-controlled trial to determine the safety and efficacy of inhaled SNG001 (IFN-β1a for nebulisation) for the treatment of patients with confirmed SARS-CoV-2 infection

Compound:	IFN-β1a (for inhalation)
Compound Name:	SNG001
Protocol Number:	SG016
Version and Date:	6, 8th June 2020

SYNAIRGEN RESEARCH LTD

CLINICAL STUDY PROTOCOL SG016

Study Title:	A randomised, double-blind, placebo-controlled trial to determine the safety and efficacy of inhaled SNG001 (IFN-β1a for nebulisation) for the treatment of patients with confirmed SARS-CoV-2 infection
Protocol Number:	SG016
Investigational Product:	SNG001 IFN-β1a
Sponsor:	Synairgen Research Ltd Level F (810) South Block, Southampton General Hospital Tremona Road, Southampton, SO16 6YD, UK
Development Phase:	Pilot to Pivotal
Sponsor's Medical Monitor:	Marcin Mankowski
Chief Investigator:	Professor Tom Wilkinson
Deputy Chief Investigator:	Professor Nick Francis

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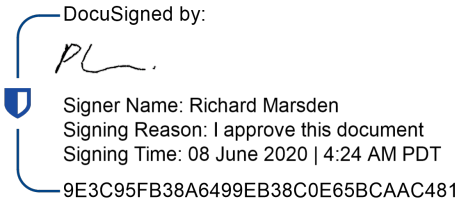
STUDY PROTOCOL SG016 - PROTOCOL SIGNATURE PAGE

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 and the Deputy 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 Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP), the standards set out by the Research Governance Framework, The Medicines for Human Use (Clinical Trials) Regulations 2004 and the Ethical principles that have their origin in the Declaration of Helsinki.

Signature:



Name (PRINT): Richard Marsden

Title: Chief Executive Officer

Date of signature: 08 June 2020 | 4:24 AM PDT

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STUDY PROTOCOL SG016 - 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 and the Deputy 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 Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP), the standards set out by the Research Governance Framework, The Medicines for Human Use (Clinical Trials) Regulations 2004 and the Ethical principles that have their origin in the Declaration of Helsinki.

Signature:

DocuSigned by:
Marcin Mankowski
Signer Name: Marcin Mankowski
Signing Reason: I approve this document
Signing Time: 08 June 2020 | 4:09 AM PDT
68CAB9DB86FC41A18CEF15571BD4C926

Name (PRINT): Marcin Mankowski

Title: Acting CMO

Date of signature: 08 June 2020 | 4:09 AM PDT

SYNAIRGEN RESEARCH LTD

CLINICAL STUDY PROTOCOL SG016 - 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 and the Deputy 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 Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP), the standards set out by the Research Governance Framework, The Medicines for Human Use (Clinical Trials) Regulations 2004 and the Ethical principles that have their origin in the Declaration of Helsinki.

Signature:

DocuSigned by:
Tom Wilkinson
Signer Name: Tom Wilkinson
Signing Reason: I approve this document
Signing Time: 08 June 2020 | 2:10 AM PDT
C61D5200A1B1471FA280272AF4BD82FB

Name (PRINT): Professor Tom Wilkinson

Title: Chief Investigator

Date of signature: 08 June 2020 | 2:10 AM PDT

SYNAIRGEN RESEARCH LTD

CLINICAL STUDY PROTOCOL SG016 - PROTOCOL SIGNATURE PAGE

DEPUTY 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 and 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 Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP), the standards set out by the Research Governance Framework, The Medicines for Human Use (Clinical Trials) Regulations 2004 and the Ethical principles that have their origin in the Declaration of Helsinki.

Signature:

Name (PRINT): Professor Nick Francis

Title: Deputy Chief Investigator

Date of signature: 08 June 2020 | 3:05 AM PDT

PRINCIPAL INVESTIGATOR

I confirm that I have read and agreed this protocol and its contents. I understand that all information concerning IFN-β1a (for inhalation) 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 Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP), the standards set out by the Research Governance Framework, The Medicines for Human Use (Clinical Trials) Regulations 2004 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 trial to determine the safety and efficacy of inhaled SNG001 (IFN-β1a for nebulisation) for the treatment of patients with confirmed SARS-CoV-2 infection

Protocol number: SG016

Study centres: Multi-national and multicentre

Number of randomised patients:
Pilot phase – 100 patients randomised in the hospital setting
– 120 patients randomised in the home setting.
Pivotal phase – estimated at an additional 100 to 300 patients per arm, but the actual number will be determined after the data review at the end of the pilot phase.
Randomised 1:1 (SNG001: placebo)

Study period: 2020 onwards	**Phase of development**: Pilot to Pivotal

Background:

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. Interferon beta (IFN-β) driven anti-viral responses have been shown to be compromised/deficient in older people[1] and those with chronic airways diseases[2,3]. These, and other patient groups are at high risk of developing severe LRT illness which can be fatal[4]. 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) delivered via a breath actuated nebuliser. 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.

SNG001 has been shown to inhibit a broad range of viruses in cell-based assays. Of particular relevance, SNG001 has been shown to inhibit viral shedding following MERS-CoV infection in cell-based assays, with a similar potency to that reported in the literature and against other virus types [5–17].
In all clinical trials conducted to date (including 3 completed trials in asthma and one ongoing trial in chronic obstructive pulmonary disease [COPD]), inhaled SNG001 has upregulated lung antiviral biomarkers in sputum for 24 hours after dosing, confirming successful delivery of biologically active drug to the lungs, demonstrating proof-of-mechanism, and supporting dose selection [18,19.]

SNG001 has been well tolerated in all clinical studies to date. Around 230 patients have been treated with SNG001, of whom around 85% were asthma or COPD patients with an active respiratory viral infection (rhinovirus, influenza, coronavirus etc). SNG001 is pH neutral, rather than acidic. A low pH is known to trigger cough. In Phase II trials in asthmatics, cough occurred in <10% of patients and the incidence was no different to that seen with placebo. SNG001 does not contain excipients such as mannitol, human serum albumin (HAS) and arginine, which are present in the injectable IFN-β formulations. SNG001 is delivered using either the I-neb or Ultra nebuliser made by Philips Respironics and Aerogen, respectively. Both devices have been tested to ensure the drug retains its activity after aerosolization. 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.

We propose to promptly treat patients with confirmed SARS-CoV-2 infection with SNG001 to prevent/reduce the severity of LRT illness. Initially, in the pilot phase of the study, 100 hospitalised patients and 120 ambulatory patients will be randomised to receive SNG001 or placebo on a 1:1 basis. A confirmatory/pivotal phase in the hospital and/or home settings may follow on from the pilot phase. The decision to go ahead with the pivotal phase will be determined after the data review at the end of the pilot phase.

The primary endpoint is prevention of severe LRT illness as determined by step movement within the 9-point Ordinal Scale for Clinical Improvement[21]. The appropriateness of this endpoint will be assessed by a blinded steering committee at the end of the pilot phase and will be changed if needed for the pivotal phase.

Demonstration of efficacy would support the use of SNG001 to treat and prevent development of severe LRT illness due to SARS-CoV-2.

Purpose of the study: The purpose of this study is to confirm that SNG001 can prevent/limit the worsening of severe LRT illness in the context of SARS-CoV-2. Safety and efficacy will be assessed.

Study Population:

Hospital setting: adults, ≥18 years of age with SARS-CoV-2 infection confirmed by a positive virus test for SARS-CoV-2 using a molecular assay e.g. Reverse Transcription Polymerase Chain Reaction (RT-PCR) or a positive point-of-care test in the presence of strong clinical suspicion of SARS-CoV-2 infection will be included in this trial.

Home Setting: high-risk adults ≥50 years of age with strong clinical suspicion of SARS-CoV-2 infection confirmed by a positive virus test for SARS-CoV-2 using a molecular assay e.g. RT-PCR will be included in this trial.

Study Design:

Hospitalised adults, ≥18 years of age, with confirmed or suspected SARS-CoV-2 infection, or non-hospitalised, high-risk patients ≥50 years of age with confirmed SARS-CoV-2 infection will be randomised to receive SNG001 or placebo. The first dose of SNG001 or placebo will be administered as soon as possible, ideally within 12 hours of confirmation of infection with SARS-CoV-2 by a positive virus test for SARS-CoV-2 using a molecular assay e.g. RT-PCR or a positive point-of-care viral infection test and definitely within 24 hours. SNG001 or placebo will be administered via the I-neb or Ultra nebuliser. Patients will receive a dose of SNG001 or placebo once a day for 14 days. All patients will give informed consent for the study. Study data will be collected from patients daily, as per the study schedule. Adverse events (AEs) and concomitant medications will be monitored throughout the study period. Serious AEs (SAEs) will be recorded until the follow-up.

To ensure patient safety, a Data Safety Monitoring Committee (DSMC) will be available to review and assess safety data/information as and when required.

The pilot phase of the trial for hospitalised patients will complete when 100 patients have been randomised in the hospital setting. The pilot phase for ambulatory patients will complete when approximately 120 high-risk patients have been randomised in the home setting. A review of safety and efficacy data will be completed. This will allow for a review of endpoints and sample sizes for the pivotal phase in the hospital and/or home settings, which is estimated to recruit an additional 100 to 300 patients per arm.

Efficacy will be determined though differences between the groups in the Ordinal Scale for Clinical Improvement scores, a scoring system which is expected to reflect severity of LRT illness, and the secondary endpoints.

Study Objectives

a. To evaluate and compare the efficacy of SNG001 versus placebo in patients with confirmed or suspected SARS-CoV-2 infection.
b. To assess the general safety and tolerability of SNG001 compared to placebo when administered to patients with confirmed or suspected SARS-CoV-2 infection.
c. To gain information from the pilot phase of the study in order to inform the design of the pivotal phase.

Study Endpoints

Primary Endpoint:

a. Change in condition measured using the Ordinal Scale for Clinical Improvement during the dosing period.

Secondary Endpoints:

a. Progression to pneumonia, as diagnosed by chest x-ray, if no pneumonia is present at time of enrolment (hospital setting only).
b. Evolution of pneumonia, as diagnosed by chest x-ray, if pneumonia is present at time of enrolment (optional, hospital setting only).

c. Time to clinical improvement (hospital setting only), defined as:
    I. Hospital discharge OR
    II. National Early Warning Score (NEWS)2 of ≤ 2 maintained for 24 hours.
d. Time to clinical improvement (home setting only), defined as:
    I. Temperature ≤37.8 °C AND
    II. COVID-19 symptoms (breathing, cough, sputum, muscle aches, headache, fatigue, sore throat, loss or change to sense of smell and/or taste, rhinorrhoea and anorexia) all rated as absent or mild.
e. Proportion of patients with clinical improvement on Day 7 and End of Treatment (hospital and home setting).
f. NEWS2 assessment of acute-illness severity (hospital setting only).
g. Time to improvement of COVID-19 symptoms (fever, breathing, cough, sputum, muscle aches, headache, fatigue, sore throat, loss or change to sense of smell and taste, rhinorrhoea and anorexia) (home setting only).
h. Time to self-reported recovery (home setting only).
i. Self-reported daily rating of overall feeling of wellness (home setting only).
j. Quality of life measured using EQ-5D-5L (home setting only).
k. Changes in daily breathlessness, cough and sputum scale (BCSS) score during the study period (including disaggregated scores).
l. Virus clearance/load (if samples are available)
    I. Time to virus clearance
    II. Viral load.
m. Safety and tolerability – vital signs, adverse events and concomitant medications.
n. Blood and sputum biomarkers (if samples are available).
o. Contact with health services, including need for hospitalisation (home setting only).
p. Consumption of antibiotics (home setting only).

Main Inclusion and Exclusion Criteria

Inclusion criteria:

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

1. A. Hospital setting: positive virus test for SARS-CoV-2 using RT-PCR, or positive point-of-care viral infection test in the presence of strong clinical suspicion of SARS-CoV-2 infection.
   B. Home setting: positive virus test for SARS-CoV-2 using a molecular assay e.g. RT-PCR in the presence of strong clinical suspicion of SARS-CoV-2 infection.
2. Male or female, ≥18 years of age (hospital setting) or ≥50 years of age (home setting) at the time of consent.
3. A. Hospital setting: patients admitted to hospital due to the severity of their confirmed or suspected COVID-19 disease OR

B. Home setting: non-hospitalised patients from high-risk groups, defined as ≥65 years of age, or ≥50 years of age and with any of the following risk factors:

- Arterial hypertension
- Cardiovascular disease
- Diabetes mellitus
- Chronic lung disease
- Chronic kidney disease (eGFR <60 mL/min/1.73m^2)
- Chronic liver disease
- Immunodeficiency due to a serious illness or medication
- Cerebrovascular disease
- Malignancy (except basal cell carcinoma) diagnosed in the last 5 years
- Body Mass Index ≥30

who present with clinical symptoms consistent with COVID-19:

- High temperature and/or
- New, continuous cough.
- Loss or change to sense of smell and/or taste

4. Provide informed consent.

5. A. Hospital setting: hospitalised female patients must be ≥1 year post-menopausal, surgically sterile, or using an acceptable method of contraception. Acceptable birth control methods are 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, intravaginal device (e.g., ethinylestradiol and etonogestrel), desogestrel (e.g., Cerazette™), total sexual abstinence and vasectomised sexual partner. Women 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 acceptable birth control method (except for the practice of total sexual abstinence), 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.

   Women not of childbearing potential are defined as women who are either permanently sterilized (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 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.

B. Home setting: non-hospitalised female patients must be ≥1 year post-menopausal or surgically sterile

Exclusion Criteria

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

1. >24 hours after confirmation of SARS-CoV-2 infection by a molecular assay e.g. RT-PCR test (hospital and home settings) or >24 hours after a positive point-of-care viral infection test (hospital setting only). This criterion does not apply to patients in the hospital setting who had their positive RT-PCR test for SARS-CoV-2 performed prior to hospitalisation.
2. >96 hours from onset of COVID-19 symptoms (cough and/or fever and/or loss or change to sense of smell and/or taste; home setting only).
3. 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.
4. 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.
5. Ventilated or in intensive care.
6. Inability to use a nebuliser with a mouthpiece.
7. History of hypersensitivity to natural or recombinant IFN-β or to any of the excipients in the drug preparation.
8. 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 0.65 mL of drug product solution containing 12 MIU/mL of IFN-β1a.

The I-neb nebuliser, fitted with a 0.53 mL chamber is filled with the contents of 1 syringe. The Ultra device is filled with the contents of two syringes. Patients inhale one dose per day.
Duration of Treatment: Patients will receive a dose of study medication once a day for 14 days.
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) and will be administered once daily via the I-neb or Ultra nebuliser.

Table 1: Study Schedule

	Hospital setting				Home setting			
	Pre-Treatment Phase	**Treatment Phase[1]**	**End of Treatment**	**Follow-up**	**Pre-Treatment Phase**	**Treatment Phase[1]**	**End of Treatment**	**Follow-up**
Assessment Days	**Day 1**	**Days 2 to 14[2]**	**24 hours after last dose or permanent treatment discontinuation (+1 day)[2]**	**14 days after last dose (+/- 3 days)[2]**	**Day 1**	**Days 2 to 14[2]**	**24 hours after last dose or permanent treatment discontinuation (+1 day)[2]**	**14 days after last dose (+/- 3 days)[2]**
Informed consent	X				X			
Point-of-care viral infection test[3]	X							
Inclusion / Exclusion criteria	X				X			
Medical history	X				X			
SARS-CoV-2 infection history	X				X			
Patient demographics	X				X			
Physical examination	X[4]	X[5,6]	X[5]					
Respiratory and other assessments[7]	X	X[5]	X[5]		X	X	X	X
Assessment of COVID-19 symptoms[8]					X	X	X	X
Vital signs	X[9]	X[5,9]	X[5,9]		X[10]	X[10]	X[10]	
Level of consciousness or new confusion[11]	X	X[5]	X[5]					
Clinical Frailty Scale	X				X			
Urine pregnancy test	X							
12-lead ECG	X		X[5]					
Chest X-ray[12]	X		X[5]					
Complications and treatment assessment			X[13]				X	
Blood sampling: Safety screen[14]	X		X[5]					
Nose or throat swab[15]	X	X	X		X			
Spontaneous sputum sample[16]	X	X	X		X	X	X	
Blood samples for biomarker assessement[15]	X	X	X		X	X	X	
Randomisation	X				X			

	Hospital setting				Home setting			
	Pre-Treatment Phase	**Treatment Phase[1]**	**End of Treatment**	**Follow-up**	**Pre-Treatment Phase**	**Treatment Phase[1]**	**End of Treatment**	**Follow-up**
Assessment Days	**Day 1**	**Days 2 to 14[2]**	**24 hours after last dose or permanent treatment discontinuation (+1 day)[2]**	**14 days after last dose (+/- 3 days)[2]**	**Day 1**	**Days 2 to 14[2]**	**24 hours after last dose or permanent treatment discontinuation (+1 day)[2]**	**14 days after last dose (+/- 3 days)[2]**
Device training (if required)	X	X			X	X		
Dose administration	X	X			X	X		
Recording AEs and concomitant medications	X	X[13]	X[13]		X	X	X	
EQ-5D-5L					X	X[17]	X	X
Self-reported rating of overall feeling of wellness					X	X[18]	X	X
Self-reported assessment of recovery						X[18]	X	X
Outcome assessment			X[13]	X			X	X
Contact with health services						X	X	X

1 All assessments and sampling are to be carried out pre-dose
2 Patients who stop dosing (for example if they become ventilated or for any other reason) should undergo assessments according to the study schedule, if possible.
3 To be performed only if a RT-PCR test result is not available at the time of patient's recruitment on Day 1.
4 Includes chest auscultation.
5 For those hospitalised patients who have been discharged, some assessments (e.g. physical examination, ECG, chest x-ray, blood samples) may not be performed, while others (e.g. BCSS, Ordinal Scale for Clinical Improvement, selected vital signs) should be performed via phone/video link, if possible.
6 Chest auscultation only unless a full physical examination is deemed necessary by the Investigator.
7 Includes assessment for pneumonia (hospital setting only), BCSS and Ordinal Scale for Clinical Improvement, (hospital and home setting).
8 Includes assessment of breathing, cough, sputum, muscle aches, headache, fatigue, sore throat, loss or change to sense of smell and/or taste, rhinorrhoea and anorexia
9 Includes twice daily temperature, respiratory rate, heart rate, systolic blood pressure and oxygen saturations.
10 Includes once daily temperature and twice daily heart rate and oxygen saturations. Height and weight should be done at the End of Treatment visit only.
11 Twice daily (hospital setting only).
12 If the site has the capabilities to perform a chest x-ray, then this should only be done when required based on clinical judgement.
13 For hospitalized patients who have been discharged, these assessments should be performed via phone/video link.
14 Full blood panel to include Full Blood Count, Urea and Electrolytes, Liver Function Tests, Troponin, C-Reactive Protein.
15 Not required for the pilot phase. For the pivotal phase this is optional, depending on whether the site has the correct experience/facilities.
16 Not required for the pilot phase. For the pivotal phase this is optional, depending on whether site the patient can produce sputum and has the correct experience/facilities and time.
17 Day 7 only.
18 Daily.

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ABBREVIATIONS AND DEFINITIONS

AAD	Adaptive Aerosol Delivery
ACVPU	Alert, Confusion, Voice, Pain, Unresponsive
AE	Adverse Event
AECB	Acute Exacerbation of Chronic Bronchitis
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BAL	Bronchoalveolar lavage
BCSS	Breathlessness, Cough and Sputum Scale
BEC	Bronchial Epithelial Cells
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Disease caused by SARS-CoV-2
CR	Clinical Research Associate
CRF	Case Report Form
CRP	C-reactive Protein
CTIMP	Clinical Trial of an Investigational Medicinal Product
Delegate	A qualified member of the study team delegated to perform a task by the investigator
DLCO	Diffusing Lung Capacity for Carbon Monoxide
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECMO	Extra-corporal Membrane Oxygenation
eGFR	Estimated Glomerular Filtration Rate
FEV_1	Forced Expiratory Volume in 1 second
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLI 2012	Global Lung Function Initiative 2012
GP	General Practitioner
HCG	Human Chorionic Gonadotropin
HSA	Human Serum Albumin
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IF	Interferon
IFN-β	Interferon-beta
IMP	Investigational Medicinal Product
INEXAS	Phase II trial of SNG001 in asthma
INR	International Normalised Ratio (standardised way of monitoring blood clotting)
ITT	Intention-to-Treat
LABA	Long Acting β_2 Agonists

LAMA	Long Acting Muscarinic Antagonists
LRT	Lower Respiratory Tract
Main REC	Main Research Ethics Committee
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome-Coronavirus
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified Intention-to-Treat
MIU	Million International Units
NEWS2	National Early Warning Score (NEWS) 2
NRES	National Research Ethics Service
PCV	Packed Cell Volume
PEFR	Peak Expiratory Flow Rate
Placebo	Comparator Medication Without the Active Ingredient
R&D	Research and Development
Randomisation	Random Allocation to Treatment Group
RBC	Red Blood Cells (Erythrocytes)
REC	Research Ethics Committee
RNA	Ribonucleic Acid
RRT	Renal Replacement Therapy
RTI	Respiratory Tract Infection
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RV	Rhinovirus
SABD	Short Acting Bronchodilator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus 2
SG004	Phase I clinical trial of SNG001 in asthma
SG005	Phase II clinical trial of SNG001 in asthma
SmPC	Summary of Product Characteristics
SMS	Text Message
SOC	Standard of Care
SOP	Standard Operating Procedure
Source data	Original documents, data and record (including but not limited to: hospital records, source documentation worksheets, lab reports)
Sponsor	Company that takes responsibility for the initiation, management and financing of the trial: Synairgen Research Limited
TBM	Tidal Breathing Mode
TEAE	Treatment-Emergent Adverse Event
VAS	Visual Analogue Scale
VMT	Vibrating Mesh Technology
WBC	White Blood Cells

1 INTRODUCTION

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) driven anti-viral responses have been shown to be compromised/deficient in older people[1] and those with chronic airways diseases[2,3.] These, and other patient groups are at high risk of developing severe LRT illness which can be fatal[4]. 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) delivered via a breath actuated nebuliser. 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.

SNG001 has been shown to inhibit a broad range of viruses in cell-based assays. Of particular relevance, SNG001 has been shown to inhibit viral shedding following Middle East Respiratory Syndrome-coronavirus (MERS-CoV) infection in cell-based assays, with a similar potency to that reported in the literature and against other virus types[5-17].

In all clinical trials (3 in asthma and one in chronic obstructive pulmonary disease [COPD]) conducted to date, inhaled SNG001 has upregulated lung antiviral biomarkers in sputum for 24 hours after dosing, confirming successful delivery of biologically active drug to the lungs, demonstrating proof-of-mechanism, and supporting dose selection[18,19].

SNG001 has been well tolerated in all clinical studies to date. Around 230 patients have been treated with SNG001, of whom around 85% were asthma or COPD patients with an active respiratory viral infection (rhinovirus, influenza, coronavirus, etc). SNG001 is pH neutral, rather than acidic. A low pH is known to trigger cough. In Phase II trials in asthmatics cough occurred in <10% of patients and the incidence was no different to that seen with placebo. SNG001 does not contain excipients such as mannitol, human serum albumin (HSA) and arginine, which are present in the injectable IFN-β formulations. SNG001 is delivered using the I-neb or Ultra nebuliser made by Philips Respironics and Aerogen, respectively. Both devices have been tested to ensure the drug retains its activity after aerosolization. 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.

We propose to promptly treat patients with confirmed or suspected SARS-CoV-2 infection with SNG001 to prevent/reduce the severity of LRT illness. Initially, in the pilot phase of the study, 100 hospitalised patients and 120 ambulatory patients will be randomised to receive SNG001 or placebo on a 1:1 basis. A confirmatory/pivotal phase in the hospital and/or home settings may follow on from the pilot phase.

The primary endpoint is prevention of severe LRT illness as determined by step movement within the 9-point Ordinal Scale for Clinical Improvement[20]. The appropriateness of this endpoint will be assessed by a blinded steering committee at the end of the pilot phase and changed if needed for the pivotal phase.

Demonstration of efficacy would support the use of SNG001 to treat and prevent development of severe LRT illness due to SARS-CoV-2.

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

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

a. To evaluate and compare the efficacy of SNG001 versus placebo in patients with confirmed or suspected SARS-CoV-2 infection.

b. To assess the general safety and tolerability of SNG001 compared to placebo when administered to patients with confirmed or suspected SARS-CoV-2 infection.

c. To gain information from the pilot phase of the study in order to inform the design of the pivotal phase.

2.2 Primary Endpoints:

a. Change in condition measured using the Ordinal Scale for Clinical Improvement during the dosing period.

2.3 Secondary Endpoints:

a. Progression to pneumonia as diagnosed by chest x-ray, if no pneumonia is present at time of enrolment (hospital setting only).
b. Evolution of pneumonia, as diagnosed by chest x-ray, if pneumonia is present at time of enrolment (optional, hospital setting only).
c. Time to clinical improvement (hospital setting only), defined as:
    I. Hospital discharge OR
    II. National Early Warning Score (NEWS)2 of ≤2 maintained for 24 hours.
d. Time to clinical improvement (home setting only), defined as:
    I. Temperature ≤37.8 °C AND
    II. COVID-19 symptoms (breathing, cough, sputum, muscle aches, headache, fatigue, sore throat, loss or change to sense of smell and taste, rhinorrhoea and anorexia) all rated as absent or mild.
e. Proportion of patients with clinical improvement on Day 7 and End of Treatment (hospital and home setting).
f. NEWS2 assessment of acute-illness severity (hospital setting only).
g. Time to improvement of COVID-19 symptoms (fever, breathing, cough, sputum, muscle aches, headache, fatigue, sore throat, loss or change to sense of smell and/or taste, rhinorrhoea and anorexia) (home setting only).
h. Time to self-reported recovery (home setting only).
i. Self-reported daily rating of overall feeling of wellness (home setting only).
j. Quality of life measured using EQ-5D-5L (home setting only).

k. Changes in daily breathlessness, cough and sputum scale (BCSS) score during the study period (including disaggregated scores).
l. Virus clearance/load (if samples are available)
    I. Time to virus clearance
    II. Viral load.
m. Safety and tolerability – vital signs, adverse events and concomitant medications.
n. Blood and sputum biomarkers (if samples are available).
o. Contact with health services (home setting only).
p. Consumption of antibiotics (home setting only).

3 STUDY DESIGN

Hospitalised adults, ≥18 years of age, with a confirmed or suspected SARS-CoV-2 infection, or non-hospitalised patients ≥50 years of age with confirmed SARS-CoV-2 infection will be randomised to receive SNG001 or placebo. The first dose of SNG001 or placebo will be administered as soon as possible, ideally within 12 hours of confirmation of SARS-CoV-2 infection by a molecular assay e.g. reverse transcription polymerase chain reaction (RT-PCR) or a positive point-of-care viral infection test and definitely within 24 hours. SNG001 or placebo will be administered via the I-neb or Ultra nebuliser. Patients will receive a dose of SNG001 or placebo once a day for 14 days. All patients will give informed consent for the study. Study data will be collected from patients daily as per the study schedule. Adverse events (AEs) and concomitant medications will be monitored throughout the study period. Serious AEs (SAEs) will be recorded from Day 1 to the Follow-up Visit.

To ensure patient safety, a Data Safety Monitoring Committee (DSMC) will be available to review and assess safety data/information as and when required.

The pilot phase of the trial for hospitalised patients will complete when 100 patients have been randomised in the hospital setting. The pilot phase for ambulatory patients will complete when approximately120 high-risk patients have been randomised in the home setting. A review of safety and efficacy data will be completed. This will allow for a review of endpoints and sample sizes for the pivotal phase in the hospital and/or home settings, which is estimated to recruit an additional 100 to 300 patients per arm. The protocol will be amended as appropriate.

Efficacy will be determined though differences between the groups in the Ordinal Scale for Clinical Improvement scores, a scoring system which is expected to reflect severity of LRT illness, and the secondary endpoints.

4 PATIENT SELECTION

4.1 Criteria for Inclusion and Exclusion

4.1.1 Inclusion Criteria

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

1. A. Hospital setting: positive virus test for SARS-CoV-2 using RT-PCR, or positive point-of-care viral infection test in the presence of strong clinical suspicion of SARS-CoV-2 infection.

   B. Home setting: positive virus test for SARS-CoV-2 using a molecular assay e.g. RT-PCR in the presence of strong clinical suspicion of SARS-CoV-2 infection.
2. Male or female, ≥18 years of age (hospital setting) or ≥50 years of age (home setting) at the time of consent.
3. A. Hospital setting: patients admitted to hospital due to the severity of their COVID-19 disease OR

   B. Home setting: non-hospitalised patients from high-risk groups, defined as ≥65-years of age, or ≥50 years of age and with any of the following risk factors:

   - Arterial hypertension
   - Cardiovascular disease
   - Diabetes mellitus
   - Chronic lung disease
   - Chronic kidney disease (eGFR <60 mL/min/1.73m^2)
   - Chronic liver disease
   - Immunodeficiency due to a serious illness or medication
   - Cerebrovascular disease
   - Malignancy (except basal cell carcinoma) diagnosed in the last 5 years
   - Body Mass Index ≥30

   who present with clinical symptoms consistent with COVID-19:

   - High temperature and/or
   - New, continuous cough.
   - Loss or change to sense of smell and/or taste
4. Provide informed consent.
5. A. Hospital setting: hospitalised female patients must be ≥1 year post-menopausal, surgically sterile, or using an acceptable method of contraception. Acceptable birth control methods are 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, intravaginal device (e.g., ethinylestradiol and etonogestrel), desogestrel (e.g., Cerazette™), total sexual abstinence and vasectomised sexual partner. Women 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 acceptable birth control method (except for the practice of total sexual abstinence), 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.

Women not of childbearing potential are defined as women who are either permanently sterilized (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.
- 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.

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.

B. Home setting: non-hospitalised female patients must be ≥1 year post-menopausal or surgically sterile.

4.1.2 Exclusion Criteria

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

1. > 24 hours after confirmation of SARS-CoV-2 infection by a molecular assay e.g. RT-PCR test (hospital and home settings) or >24 hours after a positive point-of-care viral infection test (hospital setting only). This criterion does not apply to patients in the hospital setting who had their positive RT-PCR test for SARS-CoV-2 performed prior to hospitalisation.
2. >96 hours from onset of COVID-19 symptoms (cough and/or fever and/or loss or change to sense of smell and/or taste; home setting only).
3. 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.

4. 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.
5. Ventilated or in intensive care.
6. Inability to use a nebuliser with a mouthpiece.
7. History of hypersensitivity to natural or recombinant IFN-β or to any of the excipients in the drug preparation.
8. Females who are breast-feeding, lactating, pregnant or intending to become pregnant.

5 STUDY TREATMENT

5.1 Allocation to Treatment

During the pilot phase, patients in the hospital setting will be randomised to one of two treatment groups (SNG001 or placebo) in a 1:1 ratio according to a pre-specified randomisation schedule in addition to standard of care. In the home setting, device will also be included within the randomisation schedule and the patients will be randomised to one of four groups (Ultra/ SNG001, Ultra/placebo, I-neb/SNG001 or I-neb/placebo) in a 1:1:1:1 ratio.

Allocation to treatment for the pivotal phase will be decided after the pilot phase data review. It is anticipated that this will either be a 1:1 ratio as per the pilot phase or that all patients will receive SNG001.

Should a patient withdraw after receiving any study medication then the randomisation number will not be re-assigned and the patient will not be replaced. If for any reason the patient has been randomised but does not receive any study drug, this randomisation number can be re-assigned and the patient can be replaced.

5.2 Breaking the Blind

The study will be patient- and investigator-blinded. Blinding codes should only be broken in emergency situations for reasons of patient safety. In the event of a need to unblind the trial the investigator (or delegate) will be able to access the patient randomisation list 24 hours a day; a sealed copy or copies of the unblinding envelopes will be maintained at the study site in suitable location(s) known to all study site staff (one of these locations could be the Pharmacy). The location of the unblinding envelopes must be communicated to relevant study staff and documented in the Investigator Site File. As an alternative an electronic system may be used for randomisation.

A treatment assignment should only be unblinded in the case of an emergency where the knowledge of the treatment 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.

Unblinding envelopes may not be required if after the data review from the pilot phase it is decided that all patients in the pivotal phase of the study will receive SNG001.

5.3 Stopping Rules

5.3.1 Individual Patient Stopping Rules

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

- The patient withdraws consent.
- 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 Investigator/Sponsor feels that it is in the patient's best interest to be withdrawn from the trial.
- Pregnancy.
- • Other AEs reflecting a safety concern.
- Treatment code prematurely broken by the Investigator.
- Other (reason to be specified by the Investigator in the case report form [CRF]).

Continuation of treatment of patients who have been enrolled into the study based on the results of the point-of-care viral infection test in the presence of strong clinical suspicion of SARS-CoV-2 infection but have subsequently tested negative for SARS-CoV-2 by a molecular assay e.g. RT-PCR test should be discussed with the Sponsor's Medical Monitor on a case by case basis.

5.3.2 Trial Stopping Rule

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

- In the opinion of the Sponsor or Investigator, 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 IFN-β1a 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.

- Or, if recruitment is slow, at the Sponsor's discretion.

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

5.4 Description of Investigational Medicinal Product and Device

5.4.1 SNG001

The drug substance, recombinant IFN-β1a, is manufactured under Good Manufacturing Practice (GMP) conditions by Rentschler Biotechnologie GmbH, Erwin-Rentschler-Straße 21, 88471 Laupheim, Germany. 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.

5.4.2 Control Group

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.

5.4.3 Inhalation Devices

The study medication will be delivered using the I-neb or Ultra CE-marked nebulisers. The I-neb is a portable mesh nebuliser with adaptive aerosol delivery (AAD) technology marketed by Philips Respironics. The device will be used in its tidal breathing mode (TBM). In TBM the I-neb delivers short pulses of aerosol into each inhalation and requires the patient to use tidal breathing. The I-neb will be used with the 0.53 mL chamber.

The I-neb was used in the studies SG004, SG005, INEXAS and SG015.

The Ultra nebuliser is a portable mesh nebuliser marketed by Aerogen.

5.5 Dosage and Administration

All patients will take their first dose of study medication under the supervision of study staff, either face to face or during a video call.

For the first dose only, patient's oxygen saturations should be monitored prior to and post dose administration. This monitoring should be recorded on the source worksheets.

SNG001 nebuliser solution is presented in glass syringes containing 0.65 mL of drug product solution containing 12 MIU/mL of IFN-β1a. The I-neb nebuliser, fitted with a 0.53 mL chamber is filled with the contents of 1 syringe. The Ultra device is filled with the contents of two syringes.

The study medication will be administered as a once daily dose for 14 consecutive days.

The study medication should be removed from the fridge for a minimum of 15 minutes prior to taking the dose.

For patients in the hospital setting:

Dose administration will always take place under the supervision of site staff. When the patients clinical condition allows, site staff will encourage patients to fill and use the IMP independently in preparation for discharge.

For hospitalised patients who have been discharged during the Treatment Phase:

Patients will have been trained before discharge to fill the device with IMP and use it. Study staff will 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.

For patients in the home setting:

Patients will be trained during video calls to ensure that they can fill and use the device competently. Patients will be contacted daily via video call during which they will be supervised by study staff when taking their study medication. If the patient is assessed as being competent at filling and using the device, they will be able to take their daily dose of study medication prior to or after the video call.

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.

For patients in the home setting who have been hospitalised during the Treatment Phase:

Patients who initiate study treatment in the home setting and are subsequently hospitalised due to the severity of their COVID-19 or for any other reason should continue study treatment in the hospital, if possible.

5.5.1 Dose Delivery Times

It is anticipated that a dose of study medication will take 2 to 6 minutes to be delivered completely depending on the patient's inhalation/exhalation breathing pattern. Dose delivery can be paused should this be required by the patient.

5.5.2 Packaging and Labelling

SNG001 and placebo will be presented in glass syringes with needles and plungers as ready-to-use aqueous solutions. Syringes and outer containers will be labelled in accordance with regulatory requirements.

5.6 Preparation, Handling and Dispensing

5.6.1 Preparation Time

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

5.6.2 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.

5.6.3 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 worksheets that the dose has been missed.

2. Continue with any remaining doses as normal (see Section 6.6 for Withdrawal Criteria).

5.7 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 should be kept to ensure the study medication is kept between these temperatures.

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 taking daily doses at home (including hospitalised patients who were discharged) 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.

5.8 Drug Accountability

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

For patients in the hospital setting, the Investigator must maintain study medication accountability throughout the course of the study in accordance with regulatory requirements.

For patients in the home setting, when the study medication is distributed from the dispensing facility, study medication accountability is the responsibility of the Sponsor who will ensure this by oversight of the dispensing facility.

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 site staff during their daily contact.

For the hospital and home settings, the amount of study medication received, dispensed to patients and returned by the patient should be documented. The Sponsor will provide study medication accountability forms for this purpose.

Drug accountability records will include:

- Confirmation of study medication delivery to the study site or dispensing facility.
- An inventory per study site or dispensing facility of the study medication that have been provided by the Sponsor.
- An inventory of the study medication that has been provided to each patient.
- The patient's I-neb or Ultra serial number.
- The use of each dose by each patient.
- 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 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 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 will make arrangements for the return of the study medication, or will authorise their destruction by the study site.

5.9 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 patient's source worksheets.

In the event of overdose, hospitalisation should be considered (if applicable) for observation and appropriate supportive treatment should be given. The Sponsor 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.

6 STUDY PROCEDURES

6.1 Patient Numbering

Every patient that gives informed consent will be logged and given a unique patient identification number. The unique patient identification number will consist of 9 digits (2 for the study number, 3 for the country [if applicable] and site number and 4 for patient number) and will identify the patient throughout the study.

In the pilot phase, the 4-digit patient number will be assigned sequentially to each patient within each site starting with 1001 and will not be re-assigned. In the pivotal phase, the 4-digit patient number will be assigned sequentially to each patient within each site starting with 2001 and will not be re-assigned. The study number will be 16. The patient specific unique identification number will be allocated once the patient has given informed consent.

6.2 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 met the Exclusion Criteria. Re-screening of patients will be at the discretion of the Medical Monitor. If a patient is re-screened, they will keep the same patient ID number and must give informed consent again.

6.3 Study Visits

Hospitalised and non-hospitalised patients will undergo different assessments.

For patients that were in hospital and are discharged from hospital and are required to continue taking the study medication at home, they will move from following the hospitalised assessments to non-hospitalised assessments.

6.3.1 Day 1

The following assessments should be performed on Day 1 pre-dose preferably in the following order:

For patients in the hospital setting:

- Informed consent.
- Point-of-care viral infection test (to be performed if a RT-PCR test result is not available at the time of patient recruitment on Day 1).
- If the point-of-care test is positive and there is a presence of strong clinical suspicion of SARS-CoV-2 infection, the following assessments should be carried out.
- If the point-of-care test is negative, the following assessments should only be performed once a positive result from the RT-PCR virus test is confirmed.
- Medical history.
- SARS-CoV-2 infection history.
- Patient demographics.
- Physical examination (to include chest auscultation).
- Respiratory and other assessments (in the following order: 1. Ordinal Scale for Clinical Improvement, 2. BCSS, 3. Assessment for pneumonia).
- Vital signs (including blood pressure, pulse, pulse oximetry, respiratory rate and temperature).
- Level of consciousness or new confusion
- Clinical Frailty score
- Urine pregnancy test, if applicable.
- 12-lead ECG.
- Chest x-ray (If the site has the capabilities to perform a chest x-ray, then this should only be done when required, based on clinical judgement)
- Safety blood sampling (Full Blood Count, Urea and Electrolytes, Liver Function Tests, Troponin, C-Reactive Protein).
- Nose or throat swab (Not required for the pilot phase. For the pivotal phase this is optional, depending on whether site has the correct experience/facilities and time).
- Spontaneous sputum sampling (Not required for the pilot phase. For the pivotal phase this is optional, depending on whether the patient can produce sputum and the site has the correct experience/facilities and time).
- Blood samples for biomarker assessment (Not required for the pilot phase. For the pivotal phase this is optional, depending on whether site has the correct experience/facilities and time).
- Check the patient will be able to use the nebuliser.
- Check if patient fulfils eligibility criteria.

- If the patient meets the inclusion criteria and none of the exclusion criteria they should be randomised and go on to receive the first dose of study medication.
- Recording of AEs and concomitant medications.

If the patients are hospitalised, eligibility to enter the study may be aided with data captured from standard of care procedures and tests performed as part of the admission process.

For patients in the home setting:

Part 1 of consultation:

- Medical history.
- History of suspected SARS-CoV-2 infection.
- Patient demographics.
- Concomitant medications.
- Check if patient fulfils eligibility criteria.
- Informed consent.
- If the patient meets the inclusion criteria and none of the exclusion criteria, arrangements should be made for self-swabbing.
- Patients who do not have SARS-CoV-2 infection confirmed by a molecular assay e.g. RT-PCR will be informed by study personnel and will not be enrolled into the study.
- Patients who have SARS-CoV-2 infection confirmed by a molecular assay e.g. RT-PCR will be informed by study personnel and arrangements will be made for the study medication and equipment to be delivered to the patient's home.

Part 2 of consultation:

- Respiratory and other assessments (in the following order: 1. Ordinal Scale for Clinical Improvement, 2. BCSS).
- Assessment of COVID-19 symptoms (breathing, cough, sputum, muscle aches, headache, fatigue, sore throat, sense of smell and taste, rhinorrhoea and anorexia).
- Self-reported rating of overall feeling of wellness.
- EQ-5D-5L.
- Vital signs, including pulse, pulse oximetry (optional) and temperature.
- Clinical Frailty Score
- Nose or throat swab (Not required for the pilot phase. For the pivotal phase this is optional, depending on whether site has the correct experience/facilities

- Spontaneous sputum sampling (Not required for the pilot phase. For the pivotal phase this is optional, depending on whether the patient can produce sputum and the site has the correct experience/facilities and time).
- Blood samples for biomarker assessment (not required for the pilot phase. For the pivotal phase this is optional, depending on whether it is possible).
- Device training.
- Dose administration.
- Recording of adverse events and concomitant medication.

6.3.2 Days 2 to 14

The following assessments should be performed daily from day 2 to 14 even if dosing has been stopped (for example if the patient is ventilated), the assessments should continue as if the patient had continued with dosing. They should preferably be performed in the following order, pre-dose:

For patients in the hospital setting:

- Respiratory and other assessment (in the following order: 1. Ordinal Scale for Clinical Improvement, 2. BCSS, 3. Assessment for pneumonia).
- Physical examination (Chest auscultation only unless a full physical examination is deemed necessary by the Investigator).
- Vital signs (including blood pressure, pulse, pulse oximetry and temperature).
- Level of consciousness or new confusion.
- Nose or throat swab (Not required for the pilot phase. For the pivotal phase this is optional, depending on whether site has the correct experience/facilities and time).
- Spontaneous sputum sampling (Not required for the pilot phase. For the pivotal phase this is optional, depending on whether the patient can produce sputum and the site has the correct experience/facilities and time).
- Blood samples for biomarker assessment (Not required for the pilot phase. For the pivotal phase this is optional, depending on whether site has the correct experience/facilities and time).
- Device training (if required)
- Dose administration.
- Recording of adverse events and concomitant medications.
- *For hospitalised patients who have been discharged during the Treatment Phase the following should be conducted over the telephone, preferably in the following order:*

- Respiratory and other assessment (in the following order: 1. Ordinal Scale for Clinical Improvement, 2. BCSS).
- Selected vital signs if possible.
- Instruction to administer the daily dose.
- Recording of adverse events and concomitant medications.

For patients in the home setting:

- Contact with health services, including need for hospitalisation
- Respiratory and other assessments (in the following order: 1. Ordinal Scale for Clinical Improvement, 2. BCSS).
- Assessment of COVID-19 symptoms (breathing, cough, sputum, muscle aches, headache, fatigue, sore throat, sense of smell and taste, rhinorrhoea and anorexia).
- Self-reported daily rating of overall feeling of wellness.
- Self-reported assessment of recovery.
- EQ-5D-5L (day 7 only).
- Vital signs, including pulse, pulse oximetry (optional), and temperature.
- Spontaneous sputum sampling (Not required for the pilot phase. For the pivotal phase this is optional, depending on whether the patient can produce sputum and the site has the correct experience/facilities and time).
- Blood samples for biomarker assessment (not required for the pilot phase. For the pivotal phase this is optional, depending on whether it is possible).
- Dose administration.
- Recording of adverse events and concomitant medications.
- Patients who initiate study treatment in the home setting and are subsequently hospitalised due to the severity of their COVID-19 or for any other reason should have their assessment of the Ordinal Scale for Clinical Improvement, use of study medication, and self-reported overall feeling of wellness, reported by the hospital staff, family member or another nominee, if possible.

6.3.3 End of Treatment

These assessments should be performed within 24 hours (+ 1 day) of the patient's last dose or permanent discontinuation of study medication (see section 6.6 for reasons for withdrawal).

The following assessments should preferably be performed in the following order:

For hospitalised patients:

- Physical examination (to include chest auscultation).

- Respiratory and other assessment (in the following order: 1. Ordinal Scale for Clinical Improvement, 2. BCSS, 3. Assessment for pneumonia).
- Vital signs (including blood pressure, pulse, pulse oximetry, respiratory rate, temperature, height and weight)
- Level of consciousness or new confusion
- 12-lead ECG
- Chest x-ray (optional)
- Complications and treatment assessment.
- Safety blood sampling.
- Nose or throat swab (Not required for the pilot phase. For the pivotal phase this is optional, depending on whether site has the correct experience/facilities and time).
- Spontaneous sputum sampling (Not required for the pilot phase. For the pivotal phase this is optional, depending on whether the patient can produce sputum and the site has the correct experience/facilities and time).
- Blood samples for biomarker assessment (Not required for the pilot phase. For the pivotal phase this is optional, depending on whether site has the correct experience/facilities and time).
- Recording of adverse events and concomitant medications.
- Outcome assessment.
- *For hospitalised patients who have been discharged during the Treatment Phase the following should be conducted over the telephone:*
- Respiratory and other assessment (in the following order: 1. Ordinal Scale for Clinical Improvement, 2. BCSS).
- Selected vital signs if possible.
- Complications and treatment assessment.
- Outcome assessment
- Recording of adverse events and concomitant medications.

For patients in the home setting:

- Contact with health services, including need for hospitalisation
- Respiratory and other assessments (in the following order: 1. Ordinal Scale for Clinical Improvement, 2. BCSS).
- Assessment of COVID-19 symptoms (breathing, cough, sputum, muscle aches, headache, fatigue, sore throat, sense of smell and taste, rhinorrhoea and anorexia).
- Self-reported daily rating of overall feeling of wellness
- Self-reported assessment of recovery

- EQ-5D-5L
- Vital signs, including pulse, pulse oximetry (optional), temperature, height and weight.
- Complications and treatment assessment.
- Spontaneous sputum sampling (Not required for the pilot phase. For the pivotal phase this is optional, depending on whether the patient can produce sputum and the site has the correct experience/facilities and time).
- Blood samples for biomarker assessment (not required for the pilot phase. For the pivotal phase this is optional, depending on whether it is possible).
- Recording of adverse events and concomitant medications.
- Patients who initiate study treatment in the home setting and are subsequently hospitalised due to the severity of their COVID-19 or for any other reason should have their assessment of the Ordinal Scale for Clinical Improvement reported by the hospital staff, family member or another nominee, if possible.

6.3.4 Follow-up

A follow-up telephone/video call will occur 14 days (+/- 3 days) after the patient's last dose or when the last dose of study medication would have been administered if dosing was stopped (for example if the patient was ventilated). Questioning during this call will be guided by the source worksheets and SAEs will be recorded.

6.4 Unscheduled Follow-up 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. Follow-up visits will 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.

6.5 Study Visit Restrictions

There are no study visit restrictions for this study.

6.6 Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioural, or administrative reasons. 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 returns all unused study medication, and request that the patient returns for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

Study drug administration will be stopped for any of the following reasons:

- 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 Investigator feels that it is in the patient's best interest to be withdrawn from the treatment.
- The patient misses more than 4 consecutive doses.

Please refer to Sections 5.3.1 and 5.3.2 for individual patient stopping rules.

If patients are withdrawn, where possible they should attend an End of Treatment Visit which should be performed within 24 hours (+ 1 day) post their last dose or permanent discontinuation of study medication. The patient's withdrawal and/or reason for withdrawing consent will be documented in the source worksheets.

If a patient treated in the home setting is subsequently admitted to hospital, they should remain in the study at the discretion of the Investigator and treating physician. Patients should not automatically be withdrawn due to hospitalisation.

7 STUDY ASSESSMENTS

7.1 Informed Consent

After the study has been fully explained either in person or via phone/video link, 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 include written, verbal or electronic consent may be used. Each method will be discussed and approved by the Sponsor 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. 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.

7.2 Point-of-care viral infection test

A point-of-care viral infection test will be carried out (hospitalised patients only) by study staff on Day 1 after informed consent, if a result from RT-PCR is not already available at the time of patient recruitment.

7.3 Medical History

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

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

- Significant current and past medical history in the last 5 years (including hospitalisations and operations), so tonsillectomy conducted in childhood will not be applicable. Also, 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) should be taken
- Recent vaccinations

It is recommended that medical history is taken from the patients face-to-face. However, where this is not possible i.e. for non-hospitalised patients, medical history can be taken either over phone/video link and/or by review of the patient's medical notes.

7.4 SARS-CoV-2 Infection History

The patient's SARS-CoV-2 infection history will be recorded in the source worksheets by a medical doctor or qualified nurse from the study team.

The source worksheets detail questions to be asked and information to be recorded.

It is recommended that SARS-CoV-2 infection history is taken from the patients face-to-face. However, where this is not possible i.e. for patients treated in the home setting, the infection history can be taken either over phone/video link and/or by review of the patient's medical notes.

7.5 Patient Demography

Patient demographics will be recorded in the source worksheets. These will include, age, sex, and race.

7.6 Physical examination

A full physical examination will be performed at the pre-treatment visit by a medical doctor (hospital setting only).

Only chest auscultations will be performed at all other visits unless, in the Investigator's (or delegate's) opinion, there is a clinical need to perform a full physical examination.

The source worksheets provide guidance on the physical examination. Results of the examinations will be recorded in the source worksheets.

Physical examinations will then be repeated at various time points throughout the study and will also be driven by the patient's complaints upon questioning.

For hospitalised patients who have been discharged a physical examination should only be carried out at the follow-up visit, if conducted in clinic.

For patients treated in the home setting a physical examination will not be performed.

7.7 Respiratory and Other Assessments

The following assessments and should preferably be undertaken in the order below:

1. Ordinal Scale for Clinical Improvement
2. BCSS
3. Assessment for pneumonia (hospital setting only)

1. <u>Ordinal Scale for Clinical Improvement</u>

- This assessment should be carried out once a day at the same time each day (+/- 3 hours).
- 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.
- It may be carried out face to face or over the phone/video link.
- The ordinal scale score should be given based on clinical condition. If a patient is hospitalised for reasons of isolation or quarantine they should not automatically be given the score of 3, but a score which is relevant to their clinical status, which maybe for example ambulatory score 1 even if they are hospitalised.
- The applicable assessment score as well as the date should be recorded in the source worksheets.

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 ***Mild disease***	Hospitalised, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalised ***Severe disease***	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

2. Breathlessness, Cough and Sputum Score (BCSS) (Leidy *et al*, 2003a)

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

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. Total score is expressed as the sum of the three-item score, with a range of 0-12. A mean decline of 1 point on the BCSS total scale signifies a substantial reduction in symptom severity.

- This assessment should be carried out once a day at the same time each day (+/- 3 hours).
- This assessment should be completed by the patient where possible, however, if needed, the site staff can read out the questions to the patient either face-to-face or over the telephone/video link.
- For non-hospitalised patients, this assessment will be ideally recorded on paper by the patient, however alternatives may include by telephone/video link or by email.
- For hospitalised patients that are unable to complete the BCSS due to their medical condition i.e. they are receiving ventilation, the reason for non-completion should be recorded in the source worksheets.

- The applicable score (number) for each question should be recorded in the source worksheets as well as the date, time and method of assessment.
- BCSS questions and responses:

1. How much difficulty did you have breathing today?
   0 = None – unaware of any difficulty
   1 = Mild – noticeable when performing strenuous activity (e.g. running)
   2 = Moderate – noticeable even when performing light activity (e.g. bedmaking or carrying groceries)
   3 = Marked – noticeable when washing or dressing
   4 = Severe – almost constant, present even when resting

2. How was your cough today?
   0 = No cough – unaware of coughing
   1 = Rare – cough now and then
   2 = Occasional – less than hourly
   3 = Frequent – one or more times an hour
   4 = Almost constant – never free of cough or need to cough

3. How much trouble did you have due to sputum today?
   0 = None – unaware of any trouble
   1 = Mild – rarely caused trouble
   2 = Moderate – noticeable trouble
   3 = Marked – caused a great deal of trouble
   4 = Severe – almost constant trouble

3. <u>Assessment for Pneumonia</u>

- An assessment for pneumonia should be carried out by a medically qualified doctor. The assessment will only be performed in the hospital setting.
- The outcome, date and time of the assessment should be recorded in the source worksheets.

7.8 Vital Signs

Vital signs in the hospital setting include temperature, respiratory rate, heart rate, systolic blood pressure and oxygen saturations which should be recorded twice a day.

Vital signs in the home setting include temperature (recorded once a day), heart rate and oxygen saturations (recorded twice a day).

Patients treated in the home setting will record their vital signs once during a telephone call/video link with the site staff and once on their own.

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

Pulse oximetry will be measured when a good signal from the probe is evident and stable.

Height and weight should be recorded at the follow-up visit. For patients treated in the home setting, self-reported values will be accepted.

7.9 Clinical Frailty Scale

The Clinical Frailty Scale is a nine-point global frailty scale based on clinical evaluation in the domains of mobility, energy, physical activity, and function.

Rapid NICE guidance produced in response to the COVID-19 outbreak clearly outlines the importance of identifying and grading frailty using the Clinical Frailty Scale. The purpose is to identify patients who are at increased risk of poor outcomes and who may not benefit from critical care interventions.

The Clinical Frailty Scale is included in Appendix A and once assessed the appropriate score should be recorded.

7.10 Level of consciousness or new confusion

Level of consciousness will only be assessed in the hospital setting.

Assess whether the patient has new-onset confusion, disorientation and/or agitation, where previously their mental state was normal – this may be subtle. The patient may respond to questions coherently, but there is some confusion, disorientation and/or agitation.

- The ACVPU assessment score (Alert, Confusion, Voice, Pain, Unresponsive) as well as the date and time should be recorded in the source worksheets.

  0 = Patient is alert
  3 = Patient presents with new confusion, is responsive to voice, is responsive to pain or is unresponsive

If it is unclear whether a patient's confusion is 'new' or their usual state, the altered mental state/confusion should be assumed to be new until confirmed to be otherwise.

7.11 NEWS2

The NEWS2 Score only will be assessed in the hospital setting. The NEWS2 Score will be calculated by the Sponsor from source data.

- The 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[22]:
- 1 respiration rate
- 2 oxygen saturation

- 3 systolic blood pressure
- 4 pulse rate
- 5 level of consciousness or new confusion
- 6 temperature.

7.12 COVID-19 symptoms

COVID-19 symptoms will be assessed daily for patients in the home setting only. Patients will answer questions about their symptoms using a 5-point scale: 0 (none), 1 (mild), 2 (moderate), 3 (marked) or 5 (severe). Patients will be asked to rate each of the following symptoms:

- How were your muscle aches today?
- How was your headache today?
- How tired did you feel today?
- How was your sore throat today?
- How was your runny nose today?
- How was your loss of appetite today?
- How is any loss or change to your sense of smell or taste today?

Assessment of breathing, cough and sputum will be performed as part of the BCSS score.

7.13 Time to self-reported recovery

Self-reported recovery will be assessed daily for patients in the home setting only. Patients will be asked to answer the following question:

- Do you feel recovered today (i.e. do you feel that symptoms associated with COVID-19 are no longer a problem)? Yes/No

7.14 Self-reported rating of overall feeling of wellness

Self-reported overall feeling of wellness will be assessed daily for patients in the home setting only. Patients will be asked to answer the following question:

- How well are you feeling today? Please rate how you are feeling now using a scale from 1 (the worst you can imagine) to 10 (the best you can imagine).

7.15 Contact with health services

Contacts with health services, including contacts with primary care and need for hospitalisation will be assessed for patients in the home setting only.

7.16 Quality of life measured using EQ-5D-5L

The EQ-5D-5L health-related quality of life questionnaire will be completed on Day 1, Day 7, EoT Visit and Follow-up Visit for patients in the home setting only.

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.

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY
I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

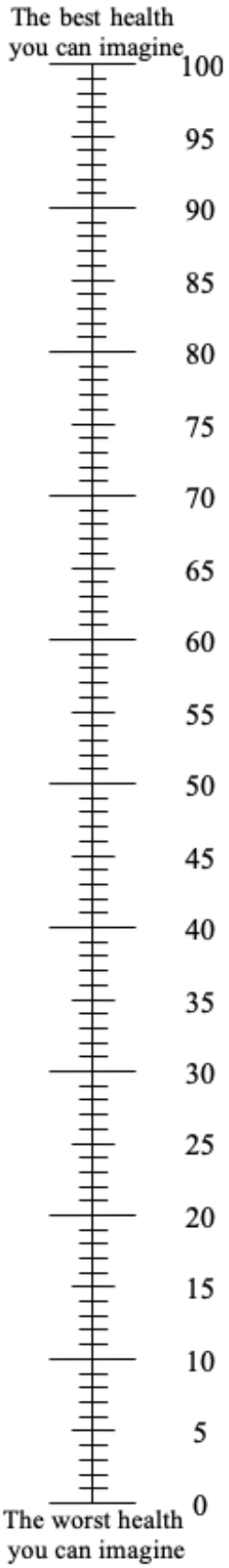
SELF-CARE
I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION
I am not anxious or depressed ❑

I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑



- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY: ☐

7.17 12-Lead ECG

ECG will only be performed in the hospital setting.

A 12-lead ECG should be performed in the supine position and it is recommended that it be taken after the patient has rested for 5 minutes.

All ECGs should be reviewed as soon as possible after recording and any clinically significant findings should be noted in the source worksheets.

ECGs should be signed and dated by the Investigator or sub-Investigator.

7.18 Chest X-ray

Chest x-ray will only be performed in the hospital setting.

If the site has the capabilities to perform a chest x-ray, then this should only be done when required based on clinical judgement.

Chest x-rays should be reviewed by the Investigator or delegate as soon as possible after being performed and the results should be recorded in the source worksheets.

Chest x-ray reports should be signed and dated by the Investigator or sub-Investigator as a way of documenting their review.

7.19 Complications and Treatment Assessment

Answers should be recorded to the questions detailed in the Source worksheets. This assessment can be completed by a medical doctor or a qualified nurse.

7.20 Samples for Laboratory Assessment

Samples for laboratory assessments will be primarily performed in hospitalised patients. Patients in the home setting may have samples collected if appropriate steps are taken to avoid contamination and protect site staff.

7.20.1 Blood Sampling: Safety Screen

For safety blood samples the following analyses will be performed (hospital setting only):

Haematology	Chemistry
Haemoglobin	Urea
Haematocrit (PCV)	Sodium
Erythrocytes (RBC)	Potassium
MCV	Creatinine
MCH	Alkaline Phosphatase
MCHC	Total Protein
WBC	Albumin
Neutrophils	Total Bilirubin
Lymphocytes	Glucose
Monocytes	ALT
Eosinophils	AST
Basophils	CRP
Platelets	Troponin

ALT: alanine transaminase; APTT: activated partial thromboplastin time; AST: aspartate transaminase; CRP: C-reactive protein; INR: international normalised ratio; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; MCV: mean corpuscular volume; PCV: packed cell volume; RBC: red blood cells; WBC: white blood cells.

Safety blood results should be reviewed by the Investigator or sub-Investigator as soon as possible.

If any results are found to be outside of the normal range and clinically significant, and the Investigator feels that the results make the patient unsuitable to continue in the study, then dosing should be stopped.

Safety bloods may be repeated for inclusion purposes, at the Investigator's discretion. Safety bloods should not be repeated more than once for the purpose of inclusion into the study.

7.20.2 Blood Biomarkers

Blood samples for biomarkers are not required to be taken during the pilot phase of the study.

During the pivotal phase, blood samples for biomarkers are optional, depending on whether site has the correct experience/facilities and time.

Where sites are able to, serum samples will be prepared for analysis of IFN-β and disease relevant biomarkers. PAXgene blood ribonucleic acid (RNA) tubes will be prepared for blood cell gene expression analysis. A laboratory manual describing the analyses, including all of the details related to laboratory procedures, will be provided separately by the Sponsor.

7.20.3 Pharmacokinetics

Blood samples for pharmacokinetics will not be taken during this study.

7.20.4 Throat Swab

Throat swabs for viral load assessment are not required to be taken during the pilot phase of the study.

During the pivotal phase, throat swabs are optional, depending on whether site has the correct experience/facilities and time.

For sites where throat swabbing can be conducted, it should be performed for hospitalised patients, taken in accordance with local guidelines and sent to the local laboratory for assessment of viral load.

For patients treated in the home setting a nose or throat swab for confirmation of SARS-CoV-2 infection should be a 'self-swab' supervised by video call and sent to the local laboratory.

7.20.5 Spontaneous Sputum Sample

Sputum samples are not required to be taken during the pilot phase of the study.

During the pivotal phase, sputum samples for biomarkers are optional, depending on whether on whether the patient can produce sputum and the site has the correct experience/facilities and time.

For sites where sputum samples are able to be collected and analysed, whenever possible patients should be encouraged to produce a spontaneous sputum sample. Samples will be primarily collected from hospitalised patients. Patients in the home setting may have sputum samples collected if appropriate steps are taken to avoid contamination and protect site staff.

Sputum samples may be processed for virology, bacteriology and biomarker response analyses. A laboratory manual describing the analyses, including all the details related to laboratory procedures, will be provided separately by the Sponsor.

7.20.6 Urine Pregnancy Testing

Early detection pregnancy strip (minimum detection 10 mIU human chorionic gonadotrophin (hCG) will be used (hospital setting only).

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 sterilized (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.

7.21 Outcome Assessment

Answers should be recorded to the questions detailed in the Source worksheets. This assessment can be completed by a medical doctor or a qualified nurse.

7.22 Concomitant Medications

Any medications taken during the study will be recorded as concomitant medications. Patients will be asked at each visit if they have taken any new concomitant medications or changed any concomitant 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.

7.23 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 in to the study, but should be aware of the possible contraindication.

Patients should be advised to refrain from receiving vaccinations during the study as these could interfere with study assessments.

8 ADVERSE EVENT REPORTING

8.1 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.
- AEs will be recorded from the date the informed consent was taken until the patient has completed their last study visit.

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.

An AE should not be recorded for the positive SAR-CoV-19 infection, this will be known at time of inclusion into the study and should be recorded as medical history.

Worsening of COVID-19 symptoms is captured as an efficacy measure and in general will not be considered an adverse event. However, if the worsening of COVID-19 symptoms meets seriousness criteria, the event will be deemed an SAE.

8.2 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 are to be captured once the first dose of study medication has been administered until the patient's last study visit (discharge/follow-up visit). TEAEs include any clinically-significant change from baseline readings in any of the study assessments.

Any abnormal result from study assessments (including laboratory findings) 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.

8.3 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 patient's condition requiring admission to the intensive care unit or mechanical ventilation 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.

8.4 Assessment of Adverse Event

The Investigator will assess every AE to determine if it is serious or not (see Section 8.3 for definition criteria). This assessment will determine the reporting procedures to be followed.

8.4.1 Relationship to Study Medication

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

8.4.1.1 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.

8.4.1.2 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.

8.5 Discontinuation of Study Medication due to an AE

Study medication may be discontinued in response to an AE at any time at the discretion of the patient and/or the Investigator. The Sponsor will be informed within 24 hours of any patient for whom this action is taken.

8.6 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 should be notified within 24 hours. Female patients should also inform the Investigator if they become pregnant within 6 months of taking part in the study. 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.

8.7 Adverse Events Recording and Reporting

8.7.1 Reporting

All AEs and TEAEs will be reported from the day informed consent is obtained until the follow up telephone/video call. This includes AEs reported as a result of study procedures. If there are ongoing AEs at the follow-up telephone/video call, every attempt should be made to follow these up until resolution or 30 days after the follow-up telephone/video call (whichever comes first).

If new AEs occur as a result of an ongoing AE, these should also be reported and recorded until resolution or 30 days after the follow-up telephone/video call (whichever comes first).

All SAEs and those non-serious AEs assessed by the Investigator (or delegate) as possibly related to the study medication should continue to be followed up even after this reporting period. Such events should be followed up until they resolve or until the Investigator assesses them as “chronic” or “stable”.

Data for AEs, TEAEs and SAEs generated after the patient’s follow-up visit will be recorded by the investigator but not necessarily reported as a part of CRF. Full details regarding AEs, TEAEs and SAEs follow-up will be described in the study report, whenever necessary.

8.7.2 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 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.

8.7.3 Reporting an Abnormal Laboratory Finding

When reporting an abnormal laboratory finding, if it is available, a clinical diagnosis should be recorded rather than the abnormal value itself (e.g. "anaemia" rather than "decreased red blood cell count" or "haemoglobin = 10.5 g/dL").

- ***Outcome***: the AE or TEAE should stop being recorded when it has either been resolved or stabilised.

- ***Management***: all measures required for the management of the AE will be recorded in the source documents.

8.8 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 an SAE form.

SAEs should be reported by the Investigator (or delegated person) to the Sponsor, using the SAE report form provided, within 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 within 24 hours or the next working day.

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

SAEs are to be followed until resolution by the Investigator 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.

In addition to informing the Sponsor, the Investigator at the study site should notify the host organisation (e.g. Research and Development [R&D]) if applicable.

The Sponsor will be responsible for informing:

- The Chief Investigator,
- The Deputy Chief Investigator
- Ethics Committee, and
- The appropriate regulatory authority, within the stipulated reporting timelines.

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

9 DATA ANALYSIS/STATISTICAL METHODS

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

9.1 Sample Size Determination

The pilot phase will have 50 patients per arm who are randomized in the hospital setting and 60 patients per arm who randomized in the home setting. The pilot phase will provide valuable insights regarding the design, conduct and analysis for the pivotal phase, including trial feasibility – recruitment rate, protocol adherence, choice of endpoints, refinement of the eligibility criteria, and more precise estimates for sample size calculations.

9.2 Randomisation

This is a double-blind study. In the pilot phase, patients in the hospital setting will be randomised to one of two treatment groups (SNG001 or placebo) in a 1:1 ratio, according to a pre-specified randomisation schedule. In the home setting, device will also be included within

the randomisation schedule and the patients will be randomised to one of four groups (Ultra/ SNG001, Ultra/placebo, I-neb/SNG001 or I-neb/placebo) in a 1:1:1:1 ratio.

Data from the different devices will be pooled for each treatment group for statistical analysis. The device is not expected to influence treatment efficacy however device will be included in relevant statistical analyses as a covariate and if the analyses indicate a positive device effect this will be investigated further. If there does not appear to be a positive device effect the covariate will be dropped from the statistical models. Further details will be provided in the Statistical Analysis Plan (SAP).

Allocation to treatment for the pivotal phase will be decided after the pilot phase data review.

9.3 Analysis Populations

The intention-to-treat (ITT) population is defined as all randomised patients who receive at least one dose of study medication. Randomised patients who do not receive study medication will not be followed up as part of the study. Re-use of randomisation numbers for those randomised who do not receive study drug will be allowed to maximise use of the limited supply of study medication. The ITT population will also be split into ITT populations for patients in the hospital and home settings, determined by the assigned cohort.

A per protocol population may be considered/defined in the SAP, both overall and separately for patients in the hospital and home settings.

The safety population is the same as the ITT population.

The modified ITT (mITT) population will include all patients within the ITT population who have SARS-CoV-2 infection confirmed by a molecular assay e.g. RT-PCR test. The mITT population will also be split into the mITT populations for patients in the hospital and home settings, determined by the assigned cohort.

All efficacy analyses will be based on the ITT populations. Patients will be analysed according to the medication they were randomised to. Further analysis may be conducted in other populations and sub-populations as defined in the SAP.

9.4 Analysis of the Dataset

9.4.1 General Definitions

A SAP will be written to detail the analyses proposed for the pilot phase of the study, this will be completed prior to unblinding and database lock (DBL) for the pilot phase. This will include the analysis of the primary endpoint and selected secondary endpoints.

Following amendment of the protocol based on results of the pilot phase a second SAP will be written detailing the full analyses for both pilot and pivotal phases of the study prior to DBL. The study period will be defined as the time from Baseline (as defined in the SAP) until the discharge/follow-up visit.

Continuous variables will be summarised using the number of values, mean, standard deviation, median, minimum and maximum values, by treatment group and overall. Changes respective to Baseline will also be evaluated where applicable. The Baseline value is the value recorded pre-treatment on day 1 unless otherwise stated in the SAP. Categorical variables will be summarised using the number and percentage of patients, by treatment group and overall.

All statistical hypothesis tests and confidence intervals performed will be two sided, using a 5% level of statistical significance. If the assumptions of any of the parametric analyses such as normality or variance homogeneity are deemed invalid, then the data may be transformed (e.g. by taking logarithms) prior to the analysis. If the assumptions are still deemed invalid, then appropriate non-parametric methods will be used instead.

Given the exploratory nature of the trial, no adjustment for multiplicity will be made.

Raw data will be listed.

There will be four instances when the blinds are broken for data analysis and reporting:

a) End of the pilot phase for hospitalised patients

b) End of the pilot phase for ambulatory patients

c) End of the pivotal phase for hospitalised patients

d) End of the pivotal phase for ambulatory patients

9.5 Analysis of Endpoints for the Pilot and Pivotal Phases

9.5.1 Pilot Phase

The number and percentage of subjects with each score on the ordinal scale for clinical improvement will be presented at baseline and each post baseline timepoint. In addition, the change in ordinal scale score from baseline will be summarised on both a categorical scale, using counts and percentages and on a continuous scale using descriptive statistics. Inferential statistical analyses such as MMRM or Mann-Whitney may be conducted in an exploratory fashion to aid the understanding of the data and the calculation of a sample size for the pivotal phase of the study. Time to event endpoints may also be defined using the Ordinal Scale for Clinical Improvement, such as time to mechanical ventilation and time to hospitalisation (for patient in the home setting only) and analysed using methods such as Cox Proportional Hazards model. Binary interpretations of the Ordinal Scale for Clinical Improvement may also be defined in the SAP, such as responders (any improvement at day 14) and complete responders (score of 0 at day 14). Composite endpoints may also be defined and analysed using appropriate methods for patients in the home setting using the Ordinal Scale for Clinical Improvement and other assessments of wellbeing such as self-reported overall feeling of wellness, self-reported assessment of recovery, COVID-19 symptoms and BCSS.

Secondary efficacy endpoints will be summarised through counts and percentages as appropriate. The medians, lower and upper quartiles of time to clinical resolution endpoints

may be calculated using the Kaplan-Meier method. Appropriate statistical models may also be defined in the SAP for other secondary endpoints to support the primary endpoint analyses. The DSMC may request further analyses.

9.5.2 Pivotal Phase

The analyses for the pivotal phase will be defined in a protocol amendment following completion of the pilot phase.

Appropriate analysis methods for each endpoint will be included in the SAP.

9.6 Safety Analysis

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

Laboratory data (haematology and blood chemistry) will be listed and summarised by time point for each treatment group and overall. Where a patient has at least one clinically significant abnormal value for a particular parameter, all values for that parameter for that patient will be identified and listed separately.

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

Concomitant medications will be summarised by Anatomical Therapeutic Chemical (ATC) class for each treatment group and overall.

9.7 Handling of Missing and Incomplete Data

Unrecorded values will be treated as missing and will not be imputed except for severity and relationship to study drug of AEs or where otherwise specified. If severity or relationship to study drug is missing, the AE will be regarded as severe or suspected, respectively. There will be no imputation of efficacy data for analyses of the pilot phase.

Missing data methods for the pivotal phase will be defined in a protocol amendment following completion of the pilot phase.

9.8 Data Safety Monitoring Committee

The DSMC will be responsible for safeguarding the interests of trial patients by assessing study data, as and when required, to provide recommendations about the progression of the trial.

The DSMC will be advisory to the Chief Investigator and the Deputy Chief Investigator, the trial sites and any other Sponsor representative. The Chief Investigator or the Deputy Chief Investigator will be responsible for promptly reviewing the DSMC recommendations, to

decide whether to continue or terminate the trial and to determine whether amendments to the protocol or changes in study conduct are required.

The DSMC may recommend that tests or procedures may be repeated to facilitate their decision-making process in order to fulfil their role.

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

The DSMC will be guided by the DSMC Charter. The Charter will define the primary responsibilities of the 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 DSMC.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Quality Control (Monitoring)

In order to ensure that quality data is collected and that sites are adhering to the protocol, International Council for Harmonisation (ICH) GCP and other guidelines and local regulations, data will be monitored at regular intervals.

The Investigator and their study team will be responsible for entering study data into the Source Worksheets provided by the Sponsor. It is the Investigator's responsibility to ensure the accuracy of the data entered in the Source Worksheets.

The Source Worksheets will act as the source documents and also the CRF. The Investigator must ensure that all Source Worksheets are completed during the study visit. Once completed, they will either be scanned and emailed to data management who will enter the data into the database or site staff will enter the data themselves directly into the database (eCRF). Any missing data or any data that requires querying with the site staff will be raised by data management or Sponsor staff.

Movement of people may be restricted, therefore, monitoring of patient medical records may be required and will be completed remotely e.g. by scanning or skype, facetime etc.

Monitoring of the data will occur as the data is being entered into the database.

In order to verify that the study is conducted in accordance with ICH GCP, regulatory requirements, and the study protocol, and that the data is authentic, accurate and complete, source data will be verified.

Upon study completion, a Close Out Visit will be conducted.

10.2 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. A Study 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 prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each patient. Study data for each enrolled patient will be entered into the Source Worksheets 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 worksheets 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 or Independent Ethics Committees (IEC) 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 The Medicines for Human Use (Clinical Trials) Regulations 2004 (including all modifications [Statutory Instruments] made since 2004). 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.

11 DATA HANDLING AND RECORD KEEPING

11.1 Source Worksheets and Case Report Form

Source Worksheets will act as the source documents and also the CRF for this study. Source Worksheets must be completed for every patient and every visit. Source Worksheets will not be monitored or entered into the database for screen failures.

11.2 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 worksheets, 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 15 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.

12 REGULATORY AND ETHICS

12.1 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 SOPs, manuals and guidelines.

12.2 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).

12.3 Independent Ethics Committee and Hospital Board Requirements

The Sponsor is responsible for ensuring 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 IEC before the study starts. If a substantial amendment is required during the study, IEC (main Research Ethics Committee [Main REC] only) approval must be obtained prior to their implementation. The Chief Investigator or the Deputy Chief Investigator are responsible for ensuring that these actions occur.

If appropriate, as well as approval by the 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 IEC, and the site's relevant hospital body, and all other necessary documentation has been received, the Sponsor 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 IEC and competent authority (if appropriate) approval.

12.4 Informed Consent and Screening Data

Patient informed consent forms will be provided by the Sponsor and submitted to the IEC. Any changes requested by the IEC must be approved by the Sponsor prior to the documents being used.

Informed consent will be obtained from each patient at Visit 1prior to any study procedures being performed and data reported.

12.5 Patient Confidentiality

The Investigator must ensure that the patients' anonymity is maintained. On the Source Worksheets 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.

12.6 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 IEC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human patients. The Sponsor will submit all protocol modifications to the required regulatory authorities.

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 a protocol deviation log.

12.7 Progress Reports and Safety Reports

The Chief Investigator should submit progress reports to the IEC and send a copy of this report to all R&D departments involved in the study annually, or more frequently if requested by either party. The progress report should be submitted 12 months after the date on which the clinical trial was given favourable opinion. Annual progress reports should continue, thereafter, until the end of the study. The Annual Progress Report Form for Clinical Trial of an Investigational Medicinal Product (CTIMP) from the National Research Ethics Service (NRES) website should be used to submit the report for sites in the UK.

Safety reports should also be submitted as required by the competent authority.

For study sites outside of the UK, the country specific requirements for progress and safety reports should be adhered to. It is the Sponsors responsibility to ensure this happens.

13 DEFINITION OF END OF TRIAL

End of Trial is defined as: Last Patient, Last Visit, in the overall study.

14 SPONSOR DISCONTINUATION CRITERIA

14.1 Study Sites

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

14.2 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 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 IEC and R&D, 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.

15 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 the study drug 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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Appendix A: Clinical Frailty Score

Clinical Frailty Scale

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3 Managing Well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4 Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9 Terminally Ill – Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia,** recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia,** they cannot do personal care without help.

SG016 – Summary of Protocol Amendments

Version Number	Changes made to create this version	Protocol Date
1	First version.	5th March 2020
2	Secondary endpoints: • Time to clinical improvement amended/clarified • NEWS2 added Inclusion criteria: • Clarification positive virus test should be via RT-PCR • Addition of high-risk co-morbidity groups • Addition of female contraception criteria Exclusion criteria: • Addition of the taking of anti-viral treatment • Addition of pregnancy etc. Study schedule amended for clarification Section 3 Study Design: SAE reporting period added Section 6.3 Study Visits: updated to reflect addition of NEWS2 and clarification around what to do if dosing stops prior to day 14. Section 6.3.4 Follow-up: clarification added Section 7 Study Assessments: NEWS2 added Section 9.4.1 General definitions: clarification that SAP will be completed prior to unblinding	16th March 2020
3	Addition of the point of care virus test and Frailty Score to the protocol. Adverse event monitoring end time amended to ensure consistency within the protocol. Study Objectives: Wording 'suspected' added to study objective a) to allow use of the point-of-care viral infection test. Inclusion criteria and Section 7.1 Informed Consent:	

	• 'written' removed from the inclusion criteria for informed consent as with COVID-19 infection control procedures, each site has differing policies on how to take informed consent. Some sites for example will not allow any paper documents into the isolation area, therefore documented verbal consent would be required here. This change allows for the different methods to be used. Section 5.3.1 Individual Patient Stopping Rules: clarification around calling the Medical Monitor regarding continuation of treatment of patients who have been enrolled into the study based on the results of the CRP/MxA point-of-care test in the presence of strong clinical suspicion of SARS-CoV-2 infection but have subsequently tested negative for SARS-CoV-2 by RT-PCR test. Section 6 Study Procedures: Clarification for site staff that throat swabs, sputum and blood samples for biomarkers are not required for the Pilot phase of the trial. Section 8.3 Serious Adverse Events: Clarification around reporting expectations for sites.	
4	Secondary Endpoints and Inclusion/exclusion criteria: clarification around which ones are applicable to the hospital setting and which ones are applicable to the home setting. Inclusion criteria: • Following wording added to contraception criteria: '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.' Synopsis, Test product, dose, and mode of administration: additional information given about the IMP and the I-neb. Section 5.5 Dosage and Administration: • monitoring of oxygen changed to prior to and post dose (the need for monitoring for an hour post dose was removed). • The following wording was also added "The study medication should be removed from the fridge for a minimum of 15 minutes prior to taking the dose." • The following wording was added "For patients in the hospital setting: Dose administration will always take place under the supervision of site staff. When the patients clinical condition allows, site staff will encourage patients to fill and use the IMP independently in preparation for discharge. For hospitalised patients who have been discharged during the Treatment Phase: Patients will have been trained before discharge to fill the device with IMP and use it. Study staff will 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.	24th April 2020

	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." Section 6.3 Study Visits and Section 7 Study Assessments: Clarification around what was to be done for the hospital setting and home setting. Section 9.3 Analysis Populations: Clarification around splitting the ITT population for the study into hospital and home settings. The following wording was added "The modified ITT (mITT) population will include all patients within the ITT population who have SARS-CoV-2 infection confirmed by RT-PCR test. The mITT population will also be split into the mITT populations for patients in the hospital and home settings, determined by the assigned cohort." Section 9.5 Analysis of Endpoints for the Pilot and Pivotal Phases: the following wording was added "Time to event endpoints may also be defined using the Ordinal Scale for Clinical Improvement, such as time to mechanical ventilation and time to hospitalisation (for patient in the home setting only) and analysed using methods such as Cox Proportional Hazards model." Other changes were only relevant to setting. "Composite endpoints may also be defined and analysed using appropriate methods for patients in the home setting using the Ordinal Scale for Clinical Improvement and other assessments of wellbeing such as self-reported overall feeling of wellness, self-reported assessment of recovery, COVID-19 symptoms and BCSS." "Appropriate statistical models may also be defined in the SAP for other secondary endpoints to support the primary endpoint analyses." Other changes were only relevant to Home setting.	
5	Exclusion criteria: • Following wording added to exclusion criteria 1: "This criterion does not apply to patients in the hospital setting who had their positive RT-PCR test for SARS-CoV-2 performed prior to hospitalisation." This allowed patients that had a positive virus test prior to hospitalisation to be randomised without the 24 hour for a positive test. • Following wording was deleted from the exclusion criteria: "Antiviral treatment (e.g. zanamivir or oseltamivir) within one week prior to randomisation and/or on the day of randomisation." Section 7.2.3 Prohibited Medications was also amended to reflect this change. Study Schedule: Following wording was added to the End of Treatment visit for clarification "or permanent treatment discontinuation". The same clarification was added to Section 6.3.3 Other changes were only relevant to the Home setting.	14th May 2020
6	Throughout the protocol when RT-PCR was written the wording "using a molecular assay e.g." was added before it. It was clarified that AE's will be monitored "throughout the study period".	8th June 2020

	Section 7.5 Demography: date of birth removed as this data was not being collected. Section 8.7.1 Adverse Event Reporting: the following wording was added "Data for AEs, TEAEs and SAEs generated after the patient's follow-up visit will be recorded by the investigator but not necessarily reported as a part of CRF. Full details regarding AEs, TEAEs and SAEs follow-up will be described in the study report, whenever necessary." Section 9.4.1 General Definitions (Analysis of the Dataset): clarification that the blinds will be broken for data analysis and reporting for the four different phases of the trial. Section 10.1 Quality Control (Monitoring): clarification around the site data entry process.	