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PROTOCOL

A phase 2, two-part study to assess the safety, antiviral biomarker responses, and efficacy of inhaled SNG001 for the treatment of patients with a confirmed respiratory virus infection undergoing invasive mechanical ventilation

Short Title:	Phase 2 study of inhaled SNG001 in mechanically ventilated patients with respiratory virus infection
Study Name:	INVENT
Compound:	IFNβ-1a (for inhalation)
Compound Name:	SNG001
Protocol Number:	SG021
EU CT Number:	2024-520375-27
Universal Trial Number:	U1111-1317-0525
Version and Date:	Version 4.0, 23 May 2025

Previous Document History:

Document	Date
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Version 2.0	29 October 2024
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CLINICAL STUDY PROTOCOL SG021

Study Title:	A phase 2, two-part study to assess the safety, antiviral biomarker responses, and efficacy of inhaled SNG001 for the treatment of patients with a confirmed respiratory virus infection undergoing invasive mechanical ventilation
Protocol Number:	SG021
Investigational Product:	SNG001 (IFNβ-1a for inhalation)
Sponsor:	Synairgen Research Ltd Level F (810) South Block, Southampton General Hospital Tremona Road, Southampton, SO16 6YD, UK
Development Phase:	Phase 2
Sponsor's Medical Officer:	[redacted]
Chief Investigator:	[redacted]

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CLINICAL STUDY PROTOCOL SG021 - 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 and the Chief Investigator, confirms the agreement of all parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Council for Harmonisation Guideline for Good Clinical Practice (ICH GCP), the standards set out by the UK Policy Framework for Health and Social Care Research, The UK Medicines for Human Use (Clinical Trials) Regulations 2004 and associated amendments, the Clinical Trial Regulation (EU) No 536/2014, the US Federal Regulations, including but not limited to 21CFR and the Ethical principles that have their origin in the Declaration of Helsinki.

Signature and Date: [redacted]

Name (PRINT): [redacted]

Title: [redacted]

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CLINICAL STUDY PROTOCOL SG021 - 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 and the Chief Investigator, confirms the agreement of all parties that the research study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Council for Harmonisation Guideline for Good Clinical Practice (ICH GCP), the standards set out by the UK Policy Framework for Health and Social Care Research, The UK Medicines for Human Use (Clinical Trials) Regulations 2004 and associated amendments, the Clinical Trial Regulation (EU) No 536/2014, the US Federal Regulations, including but not limited to 21CFR and the Ethical principles that have their origin in the Declaration of Helsinki.

Signature and Date: [redacted]

Name (PRINT): [redacted]

Title: [redacted]

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CLINICAL STUDY PROTOCOL SG021 - 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 and Sponsor's Medical Officer, confirms the agreement of all parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Council for Harmonisation Guideline for Good Clinical Practice (ICH GCP), the standards set out by the UK Policy Framework for Health and Social Care Research, The UK Medicines for Human Use (Clinical Trials) Regulations 2004 and associated amendments, the Clinical Trial Regulation (EU) No 536/2014, the US Federal Regulations, including but not limited to 21CFR and the Ethical principles that have their origin in the Declaration of Helsinki.

Signature and Date: [redacted]

Name (PRINT): [redacted]

Title: [redacted]

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CLINICAL STUDY PROTOCOL SG021 - PROTOCOL SIGNATURE PAGE

PRINCIPAL INVESTIGATOR

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

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

Signature and Date:

Name (PRINT): _____

Title: _____

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PROTOCOL SYNOPSIS

Study Title:

A phase 2, two-part study to assess the safety, antiviral biomarker responses, and efficacy of inhaled SNG001 for the treatment of patients with a confirmed respiratory virus infection undergoing invasive mechanical ventilation

Protocol Number: SG021

Study Centres: Multi-national and multi-centre.

Number of Participants:

Part 1

12 patients who have been admitted into the intensive care unit (ICU) requiring invasive mechanical ventilation (IMV) due to a respiratory virus infection will be enrolled to Cohort 1 and 12 patients will be enrolled to the optional Cohort 2.
Participants in Part 1 will be randomised 3:1 to receive either SNG001 or placebo.

Part 2

A total of 550 patients who have been admitted into the ICU requiring IMV due to a respiratory virus infection will be randomised 1:1 to receive either SNG001 or placebo.

Study Period: 2025 onwards	**Phase of Development**: Phase 2

Background:

Interferon beta (IFNβ) is a naturally occurring protein, produced by cells in response to viral infection, which orchestrates the body's antiviral responses. Respiratory viruses, including severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and influenza, have been shown to suppress the production of IFNβ to evade host immune responses. Furthermore, people who present with IFNβ deficiency due to factors including genetics, disease, age, obesity, or the presence of autoantibodies against Type I interferons, are at greater risk of developing severe disease when they contract respiratory virus infections.

Synairgen is developing SNG001, a formulation of recombinant interferon beta-1a (IFNβ-1a) solution delivered via inhalation, for the potential treatment of lower respiratory tract (LRT) viral infections. With a mechanism of action distinct from most currently available antivirals, SNG001 is a host-directed therapeutic aimed at boosting/restoring IFNβ levels (reduced due to host factors or suppressed by the virus) at the site of infection, in the lung epithelial cells to drive antiviral responses resulting in broad spectrum antiviral activity.

In the clinical setting, SNG001 has been found to:

- Boost lung antiviral responses assessed using lung antiviral biomarkers.
- Accelerate viral clearance from the lungs.
- Show potential for clinical benefit in patients with respiratory virus infections such as seasonal cold, influenza, and SARS-CoV-2 (e.g., positive signals on reducing risk of Coronavirus disease identified in 2019 (COVID-19), disease progression in hospitalised patients and reducing hospitalisation risk in out-patients).
- Be well-tolerated with a favourable safety profile in more than 750 study participants, including 342 patients with COVID-19 requiring hospitalisation and oxygen supplementation.

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There is a high unmet medical need for new broad-spectrum antiviral treatment options for the treatment of critically ill patients with confirmed viral pneumonia. In addition, mortality in mechanically ventilated patients with COVID-19 and other respiratory virus infections can reach, and in some cases exceed, 40%. Higher viral loads in ICU patients are associated with a greater need for mechanical ventilation and with higher mortality, suggesting that viral infection continues to play an important role in the ICU setting. Antiviral therapies for adult patients with respiratory virus infections are available only for influenza and SARS-CoV-2. Therefore, there is rationale to investigate whether SNG001 can offer clinical benefit in critically ill patients with a confirmed respiratory virus infection by boosting antiviral defences at the site of infection and potentially accelerate clearance of the virus.

Purpose of the Study:

The purpose of this Phase 2 study is to confirm safety of the dose of SNG001 to be administered to mechanically ventilated patients and to investigate whether SNG001 can boost antiviral defences at the site of infection in critically ill patients with a confirmed respiratory virus infection, potentially accelerating clearance of the virus and resulting in reduction in mortality rate, compared with standard of care (SOC). Safety and other efficacy endpoints will also be assessed.

Study Population:

Part 1

Adults, ≥50 years of age who are undergoing IMV for ≤48 hours due to a respiratory virus infection (confirmed by a positive virus test using a Sponsor approved rapid point of care [POC] test or SOC test) will be eligible to be enrolled into Part 1.

Part 2

Adults, ≥18 years and <50 years of age with an immunocompromising condition, or ≥50 years of age with or without immunocompromising condition, who are undergoing IMV for ≤48 hours due to a respiratory virus infection (confirmed by a positive virus test using a Sponsor approved rapid POC test or SOC test) will be eligible to be enrolled into Part 2.

Study Design:

This is a two-part, Phase 2, multi-centre, randomised study to assess the safety and efficacy of SNG001 in adult participants with a confirmed respiratory virus infection undergoing IMV.

Part 1

The primary objective of Part 1 will be to evaluate the safety of SNG001 administration to participants with a confirmed respiratory virus infection undergoing IMV.

Part 1 of this study will include a low-dose (one syringe) first cohort (Cohort 1), followed by an optional second cohort (Cohort 2) that will utilise a two-syringe dose. Each of the cohorts will consist of 12 participants, who will be randomised 3:1 to receive either SNG001 or placebo, in addition to SOC, according to a pre-specified randomisation schedule.

As a precautionary step, sentinel dosing will be conducted, where the initial two participants randomised to Cohort 1 will be randomised 1:1 (i.e. one participant will receive SNG001 and one will receive placebo). Once the first two participants have received a minimum of two doses of study medication while undergoing IMV, the Safety Review Committee (SRC) consisting, at a minimum, of the Principal Investigator (PI) or delegate, the Chief Investigator, and Synairgen's Chief Medical Officer will review the safety data and, if there are no apparent safety concerns, will approve the dosing for the remaining ten participants in Cohort 1.

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In case of a safety concern deemed by the SRC to be definitely, probably, or possibly related to the study medication is observed in one of the sentinel participants, sentinel dosing will continue in another two participants.

If a participant in the second group of two patients presents with a safety concern of the same or different nature, the study will be put on hold and the Independent Data Monitoring Committee (IDMC) will review the data and advise on study conduct.

Once dosing of all participants in Cohort 1 is completed, the data will be reviewed by the IDMC. The IDMC will advise on the conduct of the study, which may include dosing of additional participants in Cohort 1, initiation of Cohort 2 (optional), progression directly to Part 2 of the study, or study termination.

If the IDMC recommends initiation of the optional Cohort 2, sentinel dosing will be performed in the same way as described above.

For all participants in Cohort 1 and the optional Cohort 2, dosing will occur once a day for a maximum of 14 days or until hospital discharge, whichever occurs earlier.

If the optional Cohort 2 is initiated, once dosing of all participants in Cohort 2 is completed, the data will be reviewed by the IDMC. The IDMC will advise on the conduct of the study, which may include dosing of additional participants in Cohort 2, initiation of Part 2, or study termination.

Participants in Part 1 will have their pre-dose assessments conducted as per the Schedule of Assessments (SoA: Table 1). Study data will be collected as per the SoA until Day 15 or discharge from hospital, whichever comes first. A follow-up call will be performed on Day 28. In addition, a long-term follow-up call will be performed 28 days post final dose (~Day 42). Adverse events (AEs) and concomitant medications will be monitored throughout the study period.

Participants in Part 1 who receive less than two doses of study medication while undergoing IMV will be replaced.

Part 2

The primary objective of Part 2 will be to evaluate the efficacy of SNG001, versus placebo, in participants with a confirmed respiratory virus infection undergoing IMV.

Part 2 will include a total of 550 participants who will receive two syringes of either SNG001 or placebo, in addition to SOC, determined by double-blind randomisation with a ratio of 1:1.

After the first 250 participants have completed all study visits (up to and including Day 28), an interim analysis will be conducted and reviewed by the IDMC. Depending on the outcome of the analysis, the IDMC may recommend for the study to be stopped for futility or to continue recruitment. If the decision is made for the study to continue, an additional 300 participants will be enrolled.

For all participants in Part 2, daily dosing will occur for a maximum of 14 days or until hospital discharge, whichever occurs earlier.

To ensure participant safety, the IDMC will review safety data from Part 2 once 30 participants and again, once 100 participants have completed study treatment. The IDMC will also meet as and when necessary, i.e., if a safety issue arises or when the IDMC or the Sponsor request a further meeting.

Participants in Part 2 will have their pre-dose assessments conducted as per the SoA (Table 1). Study data will be collected as per the SoA until End of Study. Follow-ups will be performed on Days 28 and 42. AEs and concomitant medications will be monitored throughout the study period.

Participants in Part 2 who receive less than two doses of study medication in the initial 3 days of study treatment may be replaced.

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Study Objectives:

Part 1

Primary Objective:

To evaluate the safety of SNG001 administration to participants with a confirmed respiratory virus infection undergoing IMV.

[redacted].

Part 2

Primary Objective:

To evaluate the efficacy of SNG001 versus placebo in participants with a confirmed respiratory virus infection undergoing IMV.

Secondary Objectives:

- To evaluate the safety of SNG001 administration to participants with a confirmed respiratory virus infection undergoing IMV.
- To evaluate antiviral and biomarker responses after administration of SNG001.

Study Endpoints:

Part 1

Primary Endpoint:

The occurrence and severity of AEs and serious adverse events (SAEs), including pre-specified respiratory and cardiovascular deteriorations.

[redacted]

Part 2

Primary Endpoint:

All-cause mortality within 28 days from randomisation.

Secondary Endpoints:

a) The occurrence and severity of AEs and SAEs, including pre-specified respiratory and cardiovascular deteriorations.
b) Change from baseline in modified Sequential Organ Failure Assessment (mSOFA) score during ICU stay.
c) Time to extubation.
d) Ventilator-free days over 28 days from randomisation.
e) Duration of ICU stay.
f) Duration of hospital stay.
g) All-cause mortality within 28 days post final dose.
h) Alive and free of organ support at 28 days from randomisation and at 28 days post final dose.
i) Change in Ordinal Scale for Clinical Improvement (OSCI) score from baseline to 7, 10, 14, and 28 days post randomisation.
j) Time to first negative virus test in tracheal aspirates.
k) Change from baseline in levels of IFNβ dependent biomarkers in tracheal aspirates.

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[redacted]

Eligibility Criteria:

Part 1

Inclusion Criteria:

To be eligible for randomisation into Part 1 of this study, each participant must fulfil the following criteria:

1. Informed consent or legal representative's consent obtained.
2. Patients ≥50 years of age at the time of consent.
3. Patient admitted to the ICU and requiring IMV due to a respiratory virus infection.*
4. Presence of Influenza A (Flu A), Influenza B (Flu B), respiratory syncytial virus (RSV), rhinovirus (RV), adenovirus, parainfluenza, human metapneumovirus (HMPV), or coronaviruses (including SARS-COV-2 and seasonal coronaviruses) in a nose swab sample, confirmed by a positive virus test using a Sponsor approved rapid POC test (e.g., reverse transcription polymerase chain reaction [RT-PCR]) or SOC test via any sample type (SOC sample collected not more than 48 hours prior to intubation).**
5. Time from intubation to administration of first dose of study medication ≤48 hours.
6. Women of childbearing potential must have a negative pregnancy test. For this study, women of childbearing potential are defined as women <55 years old.

*Patients with confirmed respiratory virus infection and bacterial or fungal respiratory co-infection may be eligible for the study, providing that in the opinion of the Investigator, based on routine clinical, radiological, and microbiological assessments, the primary reason for the patient's ICU admission and IMV is their viral infection.
** The Sponsor will monitor the aetiology of viral infections during the conduct of the study and may decide to limit enrolment of patients with certain viral infections, to achieve a balanced mix of viruses.

Exclusion Criteria:

A participant must not be randomised into Part 1 of the study if they meet any of the following criteria:

1. Expected termination of IMV within 24 hours from the time of randomisation.
2. Life expectancy <24 hours.
3. Liver failure (Child-Pugh C).
4. Severe congestive heart failure (New York Heart Association [NYHA] IV).
5. Receipt of lung transplant.
6. Known or suspected active tuberculosis, or infection with other mycobacteria.
7. Known or suspected active systemic fungal infection.
8. Anticipated transfer to another hospital, which would prevent the participant from continuing in the study and completing protocol assessments.
9. Need for long-term mechanical ventilation prior to ICU admission.
10. Use of inhaled sedation.
11. Presence of tracheostomy or laryngectomy.
12. Requirement for airway pressure release ventilation mode.
13. History of hypersensitivity to natural or recombinant IFNβ or to any of the excipients in the drug preparation.

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14. Any condition, including findings in the patient's medical history or in the pre-randomisation study assessments that in the opinion of the Investigator, constitute a risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation.
15. Participation in previous clinical studies of SNG001.
16. Current or previous participation in another clinical study where the participant 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.
17. Known or suspected pregnancy.
18. Females who are breast-feeding or lactating.
19. Immunocompromising condition, including:
    - Established acquired immune deficiency syndrome (AIDS) defined as a cluster of differentiation 4 (CD4) count <200 cells/microL, and/or the presence of any AIDS-defining condition;
    - Haematological malignancy;
    - Bone marrow transplantation; or
    - Immunosuppressive therapy, including:
        - Cancer therapy (e.g. chemo-, radio-, immuno-, hormone or other types of therapy), immune-cell depleting therapy, immunosuppressive therapy for autoimmune disorders, medications for prevention of organ transplantation rejection, administered within 6 months prior to randomisation; or
        - Corticosteroids >20 mg of prednisone or equivalent per day administered continuously for >14 days prior to randomisation.
20. Severe chronic lung disease requiring home oxygen therapy, including chronic obstructive pulmonary disease, asthma, cystic fibrosis, or pulmonary fibrosis.

Part 2

Inclusion Criteria:

To be eligible for randomisation into Part 2 of this study, each participant must fulfil the following criteria:

1.a Patients ≥18 and <50 years of age at the time of consent, with an immunocompromising condition, including:
    - Solid tumour malignancy undergoing cancer therapy (e.g. chemo-, radio-, immuno-, hormone or other types of therapy);
    - Haematological malignancy in remission, with or without maintenance therapy;
    - Immunosuppressive therapy for autoimmune disease;
    - Therapy for prevention of organ transplant rejection;
    - Corticosteroids >20 mg of prednisone or equivalent per day, administered continuously for >14 days prior to randomisation.

or

1.b Patients ≥50 years of age at the time of consent, with or without an immunocompromising condition (as defined above).
2. Patient admitted to the ICU and requiring IMV due to a respiratory virus infection.*
3. Presence of Flu A, Flu B, RSV, RV, adenovirus, parainfluenza, HMPV, or coronaviruses (including SARS-COV-2 and seasonal coronaviruses) in a nose swab sample, confirmed by a positive virus test using a Sponsor approved rapid POC test (e.g., RT-PCR) or SOC test via any sample type (SOC sample collected not more than 48 hours prior to intubation).**
4. Time from intubation to administration of first dose of study medication ≤48 hours.

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5. Informed consent or legal representative's consent obtained.
6. Women of childbearing potential must have a negative pregnancy test. For this study, women of childbearing potential are defined as women <55 years old.

* Patients with confirmed respiratory virus infection and bacterial or fungal respiratory co-infection may be eligible for the study, providing that in the opinion of the Investigator, based on routine clinical, radiological, and microbiological assessments, the primary reason for the patient's ICU admission and IMV is their viral infection.
** The Sponsor will monitor the aetiology of viral infections during the conduct of the study and may decide to limit enrolment of patients with certain viral infections, to achieve a balanced mix of viruses.

Exclusion Criteria:

A participant must not be randomised into Part 2 of the study if they meet any of the following criteria:

1. Expected termination of IMV within 24 hours from the time of randomisation.
2. Life expectancy <24 hours.
3. Liver failure (Child-Pugh C).
4. Severe congestive heart failure (NYHA IV).
5. Receipt of lung transplant.
6. Known or suspected active tuberculosis, or infection with other mycobacteria.
7. Known or suspected active systemic fungal infection.
8. Immunocompromising condition, including:
   - Haematological malignancy requiring induction or consolidation therapy within 3 months prior to randomisation;
   - Bone marrow transplant within 6 months prior to randomisation;
   - Solid organ transplant within 6 months prior to randomisation;
   - Corticosteroids >75 mg of prednisone or equivalent per day, administered continuously for >7 days prior to randomisation;
   - Methotrexate therapy at randomisation, if the indication is chemotherapy for cancer;
   - Chimeric antigen receptor (CAR)-T cell therapy, administered within 3 months prior to randomisation;
   - Ibrutinib or alemtuzumab, administered within 3 months prior to randomisation;
   - Neutropenia <500/mm^3 not due to sepsis;
   - Clinical presentation consistent with severe bone marrow suppression or pancytopenia;
   - Established AIDS, defined as a CD4 count <200 cells/microL, and/or the presence of any AIDS-defining condition.
9. Anticipated transfer to another hospital, which would prevent the participant from continuing in the study and completing protocol assessments.
10. Need for long-term mechanical ventilation prior to ICU admission.
11. Use of inhaled sedation.
12. Presence of tracheostomy or laryngectomy.
13. History of hypersensitivity to natural or recombinant IFNβ or to any of the excipients in the drug preparation.
14. Any condition, including findings in the patient's medical history or in the pre-randomisation study assessments that in the opinion of the Investigator, constitute a risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation.
15. Participation in previous clinical studies of SNG001.
16. Current or previous participation in another clinical study where the participant has received a dose of an IMP containing small molecules within 30 days or 5 half-lives (whichever is

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longer) prior to entry into this study or containing biologicals within 3 months prior to entry into this study.
17. Known or suspected pregnancy.
18. Females who are breast-feeding or lactating.
19. Severe chronic lung disease requiring home oxygen therapy, including chronic obstructive pulmonary disease, asthma, cystic fibrosis, or pulmonary fibrosis.

Test Product and Dose:

SNG001 nebuliser solution is presented as a ready-to-use aqueous solution (neutral pH) in glass syringes containing [redacted] of drug product solution containing [redacted] of IFNβ-1a.

The filling of the [redacted] nebuliser will depend on the study part and cohort as follows:

- For Part 1, Cohort 1, the [redacted] nebuliser will be filled with the contents of a single syringe of SNG001 ([redacted] of SNG001 solution for inhalation containing [redacted] of IFNβ-1a) equivalent to [redacted] of IFNβ-1a.
- For Part 1, Cohort 2, the [redacted] nebuliser will be filled with the contents of two syringes of SNG001 (each syringe containing [redacted] of SNG001 solution for inhalation [redacted] of IFNβ-1a) equivalent to [redacted] of IFNβ-1a.
- For Part 2, the [redacted] nebuliser will be filled with the contents of two syringes of SNG001 (each syringe containing [redacted] of SNG001 solution for inhalation [redacted] of IFNβ-1a) equivalent to [redacted] of IFNβ-1a.

Reference Product and Dose:

The placebo nebuliser solution is presented in glass syringes containing [redacted] of solution containing the same formulation as the study medication but without IFNβ-1a (i.e., only the excipients of the SNG001 solution).

The filling of the [redacted] nebuliser will depend on the study part and cohort as follows:

- For Part 1, Cohort 1, the [redacted] nebuliser will be filled with the content of a single syringe of placebo.
- For Part 1, Cohort 2, the [redacted] nebuliser will be filled with the contents of two syringes of placebo.
- For Part 2, the [redacted] nebuliser will be filled with the contents of two syringes of placebo.

Inhalation Device and Mode of Administration:

The study medication will be delivered using the [redacted] nebuliser, a portable vibrating mesh nebuliser.

Whilst the participants undergo IMV, the [redacted] nebuliser will be used to deliver the study medication to the participant via the ventilator circuit.

In participants whose ventilatory support is de-escalated to NIV, the [redacted] nebuliser will be used via the NIV circuit (using continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP] with a non-vented mask).

Spontaneously breathing participants who were de-escalated to lower levels of oxygen supplementation (e.g., non-rebreather, Venturi or simple face masks or low-flow nasal cannula [LFNC]) or who do not require oxygen supplementation will be administered study medication via the [redacted] nebuliser in combination with the [redacted] handheld device, while receiving oxygen supplementation via LFNC and the [redacted] device oxygen port, if required.

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Administration of study medication during oxygen supplementation using high-flow nasal cannula (HFNC) is not permitted, as it is likely to result in suboptimal doses of study medication being delivered. However, participants receiving oxygen therapy using HFNC may be administered study medication by temporarily changing their respiratory support for the duration of study drug administration to:

- NIV, as described above, or
- Oxygen supplementation using LFNC (if NIV is not tolerated by the participant) and receiving study medication via the [redacted] nebuliser in combination with the [redacted] device, as described above.

Participants receiving oxygen supplementation using HFNC and who cannot tolerate either NIV or LFNC for the duration of study drug administration may need to miss their dose.

Duration of Treatment: Participants will receive study medication once a day for 14 days or until hospital discharge, whichever occurs earlier.

Duration of Study: Approximately 25 months.

Sample Size:

Part 1

Cohort 1 and the optional Cohort 2 will enrol 12 participants each.

Part 2

A sample size of 550 participants provides more than [redacted] power to detect a relative risk reduction (RRR) in mortality of [redacted]. This sample size has been calculated using a 1-sided 2.5% alpha level of superiority and assumes that [redacted] of participants randomised to placebo will die within 28 days. All deaths within 28 days of randomisation are expected to be recorded in the electronic case report form. Therefore, no adjustment for participant drop-out has been used.

This sample size allows for an interim analysis of the first 250 randomised participants for futility.

S**tatistical Methods**

Analysis Populations

The enrolled set is defined as all participants for whom informed consent has been obtained.

- The Part 1 enrolled set is defined as all participants in the enrolled set who were enrolled onto Part 1 of the study.
- The Part 2 enrolled set is defined as all participants in the enrolled set who were enrolled onto Part 2 of the study.

The intent-to-treat set is defined as all randomised participants.

The modified intent-to-treat (mITT) set is defined as all randomised participants who receive at least two doses of study medication in the initial 3 days of study treatment.

The per protocol set is defined as all participants in the mITT set who do not have any protocol deviations with an impact on efficacy.

The safety set is defined as all participants who receive at least one dose of study medication.

- The Part 1 safety set is defined as all participants in the safety set who were enrolled onto Part 1 of the study.

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- The dose escalation set is defined as all participants in the Part 1 safety set who receive at least two doses of study medication while receiving IMV

- The Part 2 safety set is defined as all participants in the safety set who were enrolled onto Part 2 of the study.

Additional analysis sets may be defined in the Statistical Analysis Plan (SAP) to support the analyses for the populations defined in the estimands.

Statistical Analysis Methodology

A SAP will be completed prior to the interim analysis.

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

Part 1 results will be summarised only, and therefore no specific estimands have been defined. The following estimands are for Part 2 of the study only.

Estimands – Part 2

Primary Estimand

All-cause mortality within 28 days from randomisation will be analysed on the mITT set using a logistic regression model with fixed effects for treatment group, site/region, virus with a positive test at enrolment, and age/immunocompromising condition status. The observed proportion of primary endpoint events will be summarised alongside the adjusted RRR, adjusted proportions, difference in adjusted proportions, and the odds ratio. If analytical issues occur due to quasi-complete or complete separation a Firth Logistic regression model will be used.

Secondary Estimands

Change from baseline in average mSOFA score will be analysed as the average change from baseline in mSOFA score both over the first 5 days after randomisation and over the entire ICU stay or until death or Day 14, if still in ICU, whichever occurs first. An analysis of covariance with fixed effects for treatment group, site/region, virus, age/immunocompromising condition status, and a covariate for baseline mSOFA score will be utilised. Missing mSOFA scores over the assessment period will not be imputed.

Time to extubation, duration of ICU stay, and duration of hospital stay will be analysed using a Cox Proportional Hazards model with fixed effects for treatment group, site/region, virus, and age/immunocompromising condition status. Ties in event times will be handled using the exact method, or the Efron approximation if computational difficulties arise. The Hazard Ratio for SNG001 versus placebo will be presented. Kaplan-Meier estimates of quartiles will also be presented.

All-cause mortality within 28 days post final dose and alive and free of organ support at 28 days from randomisation and at 28 days post final dose will be handled using similar methods to the primary analysis.

Participants who withdraw from the study prior to the occurrence of the event will be censored at the date of withdrawal. Participants who have not experienced the event at the end of the follow-up period will be censored at the date of last contact. Participants who die prior to the event will be censored at the maximum follow-up time + 1 day.

Ventilator-free days will be assessed using an ordered logistic regression using a proportional odds assumption with fixed effects for treatment group, site/region, virus, and age/immunocompromising

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condition status. The number of ventilator-free days will be calculated as 28 minus the number of days between randomisation and extubation. Participants extubated and re-intubated within 48 hours will not be considered ventilator-free on those days. Participants on a ventilator for 4 days or fewer will be grouped together, to give a maximum score of 24 days. Participants who are on a ventilator 28 days after randomisation will therefore be assigned a score of 0. Participants who die within 28 days of randomisation will be assigned a score of -1. Participants who withdraw after extubation will be assumed to be off ventilator until 28 days after ventilation. Participants who withdraw prior to extubation will be excluded from the analysis. Odds ratios for the increase in one ventilator-free day will be presented.

Change in OSCI score will be analysed using an ordered logistic regression using a proportional odds assumption with fixed effects for treatment group, site/region, virus, age/immunocompromising condition status, and baseline OSCI score. Odds ratios for a better outcome will be presented.

Time to first negative virus test will be analysed using a Cox Proportional Hazards model with fixed effects for treatment group, site/region, virus, and age/immunocompromising condition status. Ties in event times will be handled using the exact method, or the Efron approximation if computational difficulties arise. The Hazard Ratio for SNG001 versus placebo will be presented. Kaplan-Meier estimates of quartiles will also be presented.

Interim Analysis

An unblinded interim analysis will be conducted by an independent statistical team and provided to the IDMC to make a non-binding recommendation based on the criteria described in the table below. The interim analysis will be conducted after 250 participants have been enrolled and have completed the 28-day follow-up period.

Criterion	**Recommendation**
The RRR for mortality is less than [redacted]	Stop the study for futility
Otherwise	Enrol an additional 300 participants

The study may also be stopped due to other criteria, such as a low observed event rate, low probability of success or other factors. Full details of the stopping criteria will be outlined in the IDMC charter.

Analyses of some secondary efficacy endpoints may also be provided to the IDMC for consideration in any recommendation of futility in addition to the criteria above.

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Table 1: Schedule of Assessments

Assessment	Pre-Treatment[1]	Treatment Phase		End of Treatment	Follow-up	Long-term Follow-up
	Day -1	Day 1	Days 2 to 14	Within 24 hours post last dose and prior to hospital discharge	Day 28 (+2 days)	28 days post final dose (+2 days)
Informed consent	X					
Informed consent once capacity regained[2]			X	X	X	X
Inclusion/exclusion criteria	X					
Nose swab[3]	X					
Tracheal aspirate samples	X[4]	X[5]	X[5]			
Demographics	X					
Urine pregnancy test (if applicable)	X					
Medical history	X					
Physical examination	X	X[6]	X[6]	X[6]		
Height and weight (actual or estimated)	X					
Vital signs	X	X	X	X		
Randomisation	X					
OSCI	X	X	X	X	X[7]	
Ventilatory and oxygenation support parameters (including PaO_2/FiO_2 ratio or SpO2/FiO2 ratio, as applicable)	X	X	X	X		
APACHE II score	X					
mSOFA score[8]	X	X	X	X		
Recording of co-infections	X	X	X	X		
Recording of AEs and SAEs[9]	X	X	X	X	X	X
Recording of concomitant medications	X	X	X	X		
Serum sample for biomarkers and AAbs[10]		X	X			
PAXgene RNA blood sample for biomarkers[10]		X	X			
PAXgene DNA blood sample		X				
Dose administration[11]		X	X			
Duration of ICU and hospital stay					X	
Survival status					X	X
Organ support[12]					X	X

Abbreviations: AAb: autoantibody; AE: adverse event, APACHE II: Acute Physiology and Chronic Health Evaluation II; ECMO: extracorporeal membrane oxygenation; FiO_2: inspiratory oxygen concentration; ICU: intensive care unit; OSCI: Ordinal Scale for Clinical Improvement; PaO_2: partial pressure of oxygen in arterial blood; SAE: serious adverse event; mSOFA: modified Sequential Organ Failure Assessment

1. If the first dose is taken on the same day as the pre-treatment assessments, Day -1 and Day 1 assessments become one. In such a situation, all assessments scheduled for either Day -1 or Day 1 need to be performed on the same day. Assessments scheduled for both Day -1 and Day 1 should only be performed once. This includes tracheal aspirate sampling, which will be performed as a pre-dose sample prior to the first dose. If Day -1 and Day 1 assessments are performed on separate days, the Schedule of Assessments needs to be followed as specified above. The first dose should be administered as soon as possible following confirmation of consent/confirmation of eligibility and within 48 hours of intubation. For patients in ICU, who are assessed to have capacity and are consented to the study prior to the commencement of IMV, Day -1 will be the day IMV begins.
2. For participants who lack capacity and based on clinical assessment at the start of the visit.

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3. Nose swab for rapid POC viral load testing to confirm patient's eligibility Alternatively, a SOC test on a sample collected not more than 48 hours prior to intubation can be used to confirm eligibility.
4. Tracheal aspirate sample for rapid POC viral load testing (all sites, study Part 1 and Part 2, to be performed at the study site). After use for viral load testing, the tracheal aspirate sample will be processed, and frozen samples to be sent to central laboratory (to be performed by selected sites only, study Part 1 and Part 2).
5. Tracheal aspirate sample for rapid POC viral load testing (to be performed by all sites, study Part 2 only) and sample processing with frozen samples to be sent to central laboratory (to be performed by selected sites only, study Part 1 and Part 2). Sample collection to be performed daily (one sample per day) whilst the participant is undergoing invasive mechanical ventilation or until Day 7, whichever is earlier. For participants who undergo invasive mechanical ventilation for longer than 7 days sample collection for rapid POC viral load testing (to be performed by all sites, study Part 2 only) should also be performed on the last day of invasive mechanical ventilation or on Day 14, whichever is earlier. For selected sites, as agreed by the Sponsor, tracheal aspirate samples will be taken each day and a rapid POC viral load test will be completed, but full processing of the sample will only occur between Monday and Friday. For sites where a participant has been transferred to another ICU, the last day of invasive mechanical ventilation or Day 14 (whichever is earlier) sample will be omitted.
6. Physical examinations may be repeated at various time points throughout the study, as clinically indicated.
7. For participants who remain hospitalised on Day 28.
8. Daily while in the ICU.
9. Including pre-specified respiratory and cardiovascular deteriorations. All AEs and SAEs will be reported from the day informed consent is obtained until 28 days after the last administration of the study medication.
10. Daily until Day 7. For selected sites, as agreed by the Sponsor, processing of blood samples will only occur between Monday and Friday.
11. Daily while hospitalised.
12. Organ support includes the use of ventilation or oxygen supplementation, renal replacement therapy, cardiovascular system support including vasopressors and inotropes, ECMO or liver support.

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ABBREVIATIONS AND DEFINITIONS

Abbreviation/ Terms	Definition
AAb	Autoantibody
[redacted]	[redacted]
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ANCOVA	Analysis of covariance
APACHE II	Acute Physiology and Chronic Health Evaluation II
BiPAP	Bilevel positive airway pressure
CAR	Chimeric antigen receptor
CD4	Cluster of differentiation 4
COVID-19	Coronavirus disease identified in 2019 (Disease caused by SARS-CoV-2)
CPAP	Continuous positive airway pressure
CRO	Clinical Research Organisation
Ct	Cycle threshold
eCRF	Electronic case report form
ECMO	Extracorporeal membrane oxygenation
EoS	End of Study
FiO_2	Inspiratory oxygen concentration
Flu A	Influenza A
Flu B	Influenza B
GCP	Good Clinical Practice
HFNC	High-flow nasal cannula
HMPV	Human metapneumovirus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
IFNβ	Interferon-beta

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Abbreviation/ Terms	Definition
IFNβ-1a	Interferon beta-1a
IMP	Investigational Medicinal Product
IMV	Invasive mechanical ventilation
IRB	Institutional Review Board
LFNC	Low-flow nasal cannula
LRT	Lower respiratory tract
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intent-to-treat
MMRM	Mixed Model for Repeated Measures
mSOFA	Modified Sequential Organ Failure Assessment
NIV	Non-invasive ventilation
NOAEL	No-observed-adverse-effect-level
NYHA	New York Heart Association
OSCI	Ordinal Scale for Clinical Improvement
PaO_2	Partial pressure of oxygen in arterial blood
PI	Principal Investigator
Placebo	Comparator medication without the active ingredient
POC	Point of care
R&D	Research and Development
Randomisation	Random allocation to treatment group
RRR	Relative risk reduction
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcription polymerase chain reaction
RV	Rhinovirus
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SoA	Schedule of Assessments
SOC	Standard of care
SOP	Standard Operating Procedure
Source data	Original documents, data and records (including but not limited to: medical records, lab reports, etc)

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Abbreviation/ Terms	**Definition**
Sponsor	Company that takes responsibility for the initiation, management and financing of the study: Synairgen Research Limited
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse event
UK	United Kingdom

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1 INTRODUCTION

Interferon beta (IFNβ) is a naturally occurring protein, produced by cells in response to viral infection, which orchestrates the body's antiviral responses. Respiratory viruses, including severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and influenza, have been shown to suppress the production of IFNβ to evade host immune responses [1]. Furthermore, people who present with IFNβ deficiency due to their genetics [2, 3], disease [4], or other factors such as age [5], obesity [6], or the presence of autoantibodies (AAbs) against Type I interferons (IFNs) [7-9], are at greater risk of developing severe disease when they contract respiratory virus infections.

Synairgen is developing SNG001, a formulation of recombinant interferon beta-1a (IFNβ-1a) solution delivered via inhalation, for the potential treatment of lower respiratory tract (LRT) viral infections. With a mechanism of action distinct from most currently available antivirals, SNG001 is a host-directed therapeutic aimed at boosting/restoring IFNβ levels (reduced due to host factors or suppressed by the virus) at the site of infection, in the lung epithelial cells to drive antiviral responses resulting in broad spectrum antiviral activity.

SNG001 is pH neutral, rather than acidic and does not contain excipients such as mannitol, human serum albumin and arginine, which are present in the injectable IFNβ formulations and which may have their own unwanted effects if delivered to the lungs. In all previous studies, SNG001 has been delivered using vibrating mesh nebulisers.

Preclinical studies demonstrating broad spectrum, antiviral potential of SNG001 include in vitro data showing inhibition of a wide range of viruses in cell-based assays, including those which cause seasonal cold and influenza infections (e.g., respiratory syncytial virus [RSV], rhinovirus [RV], highly pathogenic viruses such as haemagglutinin 5 and neuraminidase 1 – influenza A [Flu A] virus subtype H5N1 'bird flu' and Middle East respiratory syndrome-coronavirus, and pandemic viruses such as H1N1 2009 and SARS-CoV-2 variants of concern [including Alpha, Beta, Gamma, Delta and Omicron]), as well as positive data in a non-human primate model of viral pneumonia driven by pandemic influenza (pH1N1 2009).

Clinically, across seven studies in both the out-patient and hospital setting, SNG001 has been found to:

- Boost lung antiviral responses assessed using lung antiviral biomarkers.
- Accelerate viral clearance from the lungs.
- Show potential for clinical benefit in patients with respiratory virus infections such as seasonal cold, influenza and SARS-CoV-2 (e.g., positive signals on reducing risk of coronavirus disease identified in 2019 [COVID-19], disease progression in hospitalised patients and reducing hospitalisation risk in out-patients).
- Be well-tolerated with a favourable safety profile in more than 750 study participants, including 342 patients with COVID-19 requiring hospitalisation and oxygen supplementation. No specific safety signals were observed, whether related to local tolerance or systemic effects.

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Treatment of critically ill patients with confirmed viral pneumonia constitutes a high unmet medical need. Mortality in mechanically ventilated patients with COVID-19 and other respiratory virus infections can reach, and in some cases exceed, 40% [10-15]. Higher viral loads in Intensive Care Unit (ICU) patients are associated with a greater need for mechanical ventilation and higher mortality rates [16], suggesting that viral infection continues to be a major factor in the ICU setting. Antiviral therapies for adult patients with respiratory virus infections are available only for influenza and SARS-CoV-2.

Clinical studies have shown the benefit of antiviral treatment with remdesivir administered to patients with severe COVID-19. Recently, a comparative effectiveness study including both immunocompetent and immunocompromised patients with severe or critical COVID-19 showed treatment with remdesivir significantly reduced 14-day and 28-day mortality in patients requiring high flow oxygen/non-invasive ventilation (NIV) or IMV/extracorporeal membrane oxygenation (ECMO) in the first 2 days of hospitalisation, indicating that antivirals have the potential for clinical benefit in critically ill patients [17].

This SG021 study is designed to assess the efficacy and safety of SNG001 delivered to patients undergoing invasive mechanical ventilation (IMV) at a dose delivered to the lungs that is comparable to that delivered in previous studies to spontaneously breathing patients.

Non-clinical data support a maximum lung delivered dose per day to humans of [redacted] ([redacted] assuming a conservative 60 kg human body weight. This dose is based on the no-observed-adverse-effect-level (NOAEL) from the Good Laboratory Practice (GLP) repeat dose 14-day toxicity study in cynomolgus monkey of [redacted]/day total inhaled dose, which corresponds to [redacted]/day lung deposited dose, assuming a lung deposition fraction of 25%.

A dose escalating trial in asthmatic patients (SG004; [18]) using the I-neb nebuliser established that administration of a single syringe (with each syringe containing a nominal volume of [redacted] SNG001 solution containing [redacted] of IFNβ-1a; equivalent to [redacted] of IFNβ-1a) resulted in the lung delivered dose of approximately [redacted] of IFNβ-1a and induced an antiviral response in the lungs that was present 24 hours after dose administration.

For subsequent efficacy and safety studies in spontaneously breathing patients with COVID-19 (SG016, SG018; [18]) using the [redacted] nebuliser in combination with the [redacted] handheld device, administration of two syringes delivered a lung dose of approximately [redacted]. That offers a 4.2-fold safety margin between the NOAEL in monkeys and the two syringes dose delivered via [redacted] nebuliser, based on comparative lung exposure (mg/g lung) and using the FDA-accepted method by Tepper et al [19].

Comparison of biomarker upregulation data from previously conducted studies (SG015; [18]) shows that treatment with the target dose of 2 syringes of SNG001 ([redacted] of IFNβ-1a) in non-infected patients elicits comparable biomarker upregulation to the physiological biomarker response observed in patients with a respiratory virus infection (prior to the administration of SNG001). In the clinical studies conducted in infected patients (SG005; INEXAS; SG015; [18]), the initial biomarker response has been shown to decline in patients treated with placebo, whereas treatment with SNG001 maintained this physiological level of biomarker response triggered by the virus until the end of the treatment period. Importantly, these studies showed

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that the maintained upregulation of biomarkers in the respiratory tract observed in patients treated with SNG001 was associated with faster viral clearance and improvements in lung function compared to placebo.

In the SG021 study, SNG001 will be delivered to patients undergoing IMV via the ventilator. Subsequently, as patients' status improves their ventilatory support is de-escalated to non-invasive ventilation (NIV), SNG001 will be delivered via the NIV circuit (using continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP] with a non-vented mask). Drug delivery in patients undergoing IMV or NIV will be achieved using the [redacted] nebuliser under the control of the [redacted] Controller [redacted] (a controller which detects the breath pattern in a ventilatory circuit and controls aerosol generation). Laboratory testing was undertaken to assess the efficiency of SNG001 administration under a range of ventilator, CPAP and BiPAP parameters and simulated patient breathing patterns, to determine the dose required to deliver an inhaled dose equivalent to that delivered to patients during previous clinical trials. Data generated in both IMV and NIV settings indicated that a two-syringe dose of SNG001 [redacted] of IFNβ-1a) administered using the [redacted] nebuliser/[redacted] controller results in at least a comparable inhaled dose to that obtained with two syringes during normal tidal breathing, using the [redacted] nebuliser [redacted] device. Since the two-syringe dose is expected to induce a robust antiviral response in the lungs, produced an efficacy signal and was well tolerated in previous clinical studies, it is considered as the target dose for administration in the SG021 study.

While SNG001 has shown a favourable safety profile in a large population of spontaneously breathing patients, it has not been administered to the most severely ill patients requiring IMV. For that reason, the current study will employ a two-part design, where a single syringe dose ([redacted] SNG001 solution containing [redacted] of IFNβ 1a; equivalent to [redacted] of IFNβ-1a), a dose lower than the target dose, will initially be administered to a cohort of patients undergoing IMV, to assess safety and tolerability. Based on the safety data from the single syringe cohort and the data from laboratory testing of drug delivery via ventilator circuit, the Independent Data Monitoring Committee (IDMC) will make a recommendation on the conduct of the study.

In conclusion, there is an urgent need for new broad-spectrum antiviral treatment options for the treatment of critically ill patients with confirmed viral pneumonia. Therefore, there is rationale to investigate whether SNG001 can offer clinical benefit in critically ill patients with a confirmed respiratory virus infection by boosting antiviral defences at the site of infection and potentially accelerating clearance of the virus.

Complete information on SNG001 is available in the Investigator's Brochure (IB) [18].

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Part 1

Primary Objective:

To evaluate the safety of SNG001 administration to participants with a confirmed respiratory virus infection undergoing IMV.

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[redacted]

Primary Endpoint:

The occurrence and severity of adverse events (AEs), and serious adverse events (SAEs), including pre-specified respiratory and cardiovascular deteriorations.

[redacted].

2.2 Part 2

Primary Objective:

To evaluate the efficacy of SNG001 versus placebo in participants with a confirmed respiratory virus infection undergoing IMV.

Secondary Objectives:

- To evaluate the safety of SNG001 administration to participants with a confirmed respiratory virus infection undergoing IMV.
- To evaluate antiviral and biomarker responses after administration of SNG001.

Primary Endpoint:

All-cause mortality within 28 days from randomisation.

Secondary Endpoints:

a) The occurrence and severity of AEs and SAEs, including pre-specified respiratory and cardiovascular deteriorations.
b) Change from baseline in modified Sequential Organ Failure Assessment (mSOFA) score during ICU stay.
c) Time to extubation.
d) Ventilator-free days over 28 days from randomisation.
e) Duration of ICU stay.
f) Duration of hospital stay.
g) All-cause mortality within 28 days post final dose.
h) Alive and free of organ support at 28 days from randomisation and at 28 days post final dose.
i) Change in Ordinal Scale for Clinical Improvement (OSCI) score from baseline to 7, 10, 14, and 28 days post randomisation.
j) Time to first negative virus test in tracheal aspirates.
k) Change from baseline in levels of IFNβ dependent biomarkers in tracheal aspirates.

[redacted]

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The following estimands are for Part 2 of the study only. Part 1 study data will be summarised only and therefore no specific estimands have been defined.

Primary Estimand

Objective	Endpoint	Estimand
To evaluate the efficacy of SNG001 versus placebo in participants with a confirmed respiratory virus infection undergoing IMV.	All-cause mortality within 28 days from randomisation.	*Population:* Participants receiving IMV who test positive for a respiratory virus infection (further described using the study eligibility criteria) who receive at least two doses of study medication within the initial 3 days of study treatment. *Treatment strategies to be compared:* Once-a-day dosing for 14 days or until hospital discharge, whichever occurs earlier: • SNG001 + Standard of Care (SOC). • Placebo + SOC. *Population-level summary measure:* relative risk reduction (RRR) conditional on the site/region of enrolment, virus, and age/immunocompromising condition status. *Intercurrent event strategies:* • Deviations from the planned treatment regimen after Day 3, the use of concomitant medications, extubation, and bacterial or fungal respiratory co-infection will be handled according to a treatment policy strategy.

Secondary Safety Estimand

Objective	Endpoint	Estimand
To evaluate the safety of SNG001 administration to participants with a confirmed respiratory virus infection undergoing IMV.	The occurrence and severity of AEs and SAEs, including pre-specified respiratory and cardiovascular deteriorations.	*Population:* Participants receiving IMV who test positive for a respiratory viral infection (further described using the study eligibility criteria) who receive at least one dose of study medication. *Treatment strategies to be compared:* Same as the primary estimand. *Population-level summary measure:* Percentages of participants reporting specific events, overall, by severity, seriousness, relatedness, and if leading to treatment discontinuation for each treatment group. *Intercurrent event strategies:* • Deviations from the planned treatment regimen, the use of concomitant medications, and extubation due to a tracheostomy will be handled using a treatment policy strategy.

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Secondary Efficacy Estimands

Objective	Endpoint	Estimand
To evaluate the efficacy of SNG001 versus placebo in participants with a confirmed respiratory virus infection undergoing IMV.	Change from baseline in average mSOFA score during ICU stay.	*Population:* Same as the primary estimand. *Treatment strategies to be compared:* Once-a-day dosing for 14 days or until discharged from the ICU or death, whichever occurs earlier: • SNG001 + SOC. • Placebo + SOC. *Population-level summary measure:* • Difference in the average change from baseline in mSOFA score over the entire ICU stay. • Difference in the average change from baseline in mSOFA score over the first 5 days after randomisation. *Intercurrent event strategies:* • Death will be handled using a composite strategy where mSOFA score will be set to the maximum observed score across all patients. • Deviations from the planned treatment regimen after Day 3, the use of concomitant medications, extubation, and bacterial or fungal respiratory co-infection will be handled according to a treatment policy strategy.
As above.	Time to extubation in days, where time of extubation is defined as the date free from all tubes (endotracheal tube and tracheostomy tube), which was sustained for a minimum of 48 hours.	*Population:* Same as the primary estimand. *Treatment strategies to be compared:* Same as the primary estimand. *Population-level summary measure:* Hazard ratio. *Intercurrent event strategies:* • Death before extubation will be handled using a composite strategy where time to extubation will be defined as the maximum observation time + 1 day. • Deviations from the planned treatment regimen after Day 3, the use of concomitant medications, bacterial or fungal respiratory co-infection, and tracheostomy will be handled according to a treatment policy strategy. • Hospital discharge within 48 hours of extubation will be handled using a composite strategy, where extubation will be assumed to have been successful.

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Objective	Endpoint	Estimand
As above.	Ventilator-free days over 28 days from randomisation, where ventilator-free is defined as free from all tubes (endotracheal tube and tracheostomy tube). Participants extubated and re-intubated within 48 hours will not be considered ventilator-free on those days.	*Population:* Same as the primary estimand. *Treatment strategies to be compared:* Same as the primary estimand. *Population-level summary measure:* Odds ratio for improvement by 1 ventilator-free day. *Intercurrent event strategies:* • Death will be handled using a composite strategy where death will be assigned the worst score of -1. • Deviations from the planned treatment regimen after Day 3, the use of concomitant medications, bacterial or fungal respiratory co-infection, and tracheostomy will be handled according to a treatment policy strategy. • Hospital discharge within 48 hours of extubation will be handled using a composite strategy where all subsequent days will be considered as ventilator-free. • Withdrawal prior to extubation will be handled using a principal stratum strategy.
As above.	Duration of ICU stay.	*Population:* Same as the primary estimand. *Treatment strategies to be compared:* Same as the primary estimand. *Population-level summary measure:* Hazard ratio. *Intercurrent event strategies:* • Death before ICU discharge will be handled using a composite strategy where duration of ICU stay will be defined as the maximum observation time + 1 day. • Deviations from the planned treatment regimen after Day 3, the use of concomitant medications, and bacterial or fungal respiratory co-infection will be handled according to a treatment policy strategy.
As above.	Duration of hospital stay.	*Population:* Same as the primary estimand. *Treatment strategies to be compared:* Same as the primary estimand. *Population-level summary measure:* Hazard ratio. *Intercurrent event strategies:* • Death before hospital discharge will be handled using a composite strategy where duration of hospital stay will be defined as the maximum observation time + 1 day.

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Objective	Endpoint	Estimand
		• Deviations from the planned treatment regimen after Day 3, the use of concomitant medications, and bacterial or fungal respiratory co-infection will be handled according to a treatment policy strategy.
As above.	All-cause mortality within 28 days post final dose.	*Population:* Participants receiving IMV who test positive for a respiratory virus infection (further described using the study eligibility criteria) who receive at least two doses of study medication within the initial 3 days of study treatment. *Treatment strategies to be compared:* Once-a-day dosing for 14 days or until hospital discharge, whichever occurs earlier: • SNG001 + SOC. • Placebo + SOC. *Population-level summary measure:* RRR conditional on the site/region of enrolment, virus, and age/immunocompromising condition status. *Intercurrent event strategies:* • Deviations from the planned treatment regimen after Day 3, the use of concomitant medications, extubation, and bacterial or fungal respiratory co-infection will be handled according to a treatment policy strategy.
As above.	Alive and free of organ support at 28 days from randomisation and at 28 days post final dose.	*Population:* Participants receiving IMV who test positive for a respiratory virus infection (further described using the study eligibility criteria) who receive at least two doses of study medication within the initial 3 days of study treatment. *Treatment strategies to be compared:* Once-a-day dosing for 14 days or until hospital discharge, whichever occurs earlier: • SNG001 + SOC. • Placebo + SOC. *Population-level summary measure:* RRR conditional on the site/region of enrolment, virus, and age/immunocompromising condition status. *Intercurrent event strategies:* • Death will be handled using a composite strategy because death would be considered a failure to achieve the endpoint. • Deviations from the planned treatment regimen after Day 3, the use of concomitant medications, ICU discharge, hospital discharge and bacterial or fungal respiratory co-infection will be handled according to a treatment policy strategy.

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Objective	Endpoint	Estimand
As above.	Change in OSCI score from baseline to 7, 10, 14, and 28 days post randomisation.	*Population:* Same as the primary estimand. *Treatment strategies to be compared:* Same as the primary estimand. *Population-level summary measure:* Odds ratio for a better outcome. *Intercurrent event strategies:* • Death will be handled using a composite strategy because death is part of the endpoint definition. • Deviations from the planned treatment regimen after Day 3, the use of concomitant medications, and bacterial or fungal respiratory co-infection will be handled according to a treatment policy strategy.
As above.	Time to first negative virus test in tracheal aspirates.	*Population:* Same as the primary estimand. *Treatment strategies to be compared:* Once-a-day dosing for 7 days or until ICU discharge or death, whichever occurs earlier: • SNG001 + SOC. • Placebo + SOC. *Population-level summary measure:* Hazard ratio. *Intercurrent event strategies:* • Death will be handled using a composite strategy where time to first negative virus test will be defined as the maximum observation time + 1 day. • Deviations from the planned treatment regimen after Day 3, the use of concomitant medications, and bacterial or fungal respiratory co-infection will be handled according to a treatment policy strategy.

Secondary Biomarker Estimand

Objective	Endpoint	Estimand
To evaluate antiviral and biomarker responses after administration of SNG001.	Change from baseline in levels of IFNβ dependent biomarkers in tracheal aspirates.	*Population:* Same as the primary estimand. *Treatment strategies to be compared:* Once-a-day dosing for 7 days or until hospital discharge or death, whichever occurs earlier: • SNG001 + SOC. • Placebo + SOC. *Population-level summary measure:* Difference in mean biomarker levels over the treatment period (Day 1 to Day 7). *Intercurrent event strategies:* • Death before hospital discharge will be handled using a composite strategy where the Day 7 evaluation will be set to the worst observed value for the patient.

Objective	Endpoint	Estimand
		• Deviations from the planned treatment regimen after Day 3, the use of concomitant medications, and bacterial or fungal respiratory co-infection will be handled according to a treatment policy strategy.

[redacted]

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[redacted]	[redacted]	[redacted]
		[redacted]
[redacted]	[redacted]	[redacted]

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3 STUDY DESIGN

Consented patients who test positive for Flu A, Influenza B (Flu B), RSV, RV, adenovirus, parainfluenza, human metapneumovirus (HMPV), or coronaviruses (including SARS-CoV-2 and seasonal coronaviruses), and are otherwise deemed eligible, will be enrolled into the study and receive the first dose of study medication no later than 48 hours after intubation and commencement of IMV. The study will consist of two parts:

3.1 Part 1

The primary objective of Part 1 will be to evaluate the safety of SNG001 administration to participants with a confirmed respiratory virus infection undergoing IMV.

Part 1 (double-blind) will include a low-dose (one syringe) first cohort (Cohort 1), followed by an optional second cohort (Cohort 2) that will utilise a two-syringe dose. Each of the cohorts will consist of 12 participants, who will be randomised 3:1 to receive either SNG001 or placebo, in addition to SOC, according to a pre-specified randomisation schedule.

As a precautionary step, sentinel dosing will be conducted, where the initial two participants randomised to Cohort 1 will be randomised 1:1 (i.e. one participant will receive SNG001 and one will receive placebo). Once the first two participants have received a minimum of two doses of study medication while undergoing IMV, the Safety Review Committee (SRC) consisting, at a minimum, of the Principal Investigator (PI) or delegate, the Chief Investigator, and Synairgen's Chief Medical Officer will review the safety data and, if there are no apparent safety concerns, will approve the dosing for the remaining ten participants in Cohort 1.

In case of a safety concern deemed by the SRC to be definitely, probably, or possibly related to the study medication is observed in one of the sentinel participants, sentinel dosing will continue in another two participants.

If a participant in the second group of two patients presents with a safety concern of the same or different nature, the study will be put on hold and the IDMC will review the data and advise on study conduct.

Once dosing of all participants in Cohort 1 is completed, the data will be reviewed by the IDMC. The IDMC will advise on the conduct of the study, which may include dosing of additional participants in Cohort 1, initiation of the optional Cohort 2, progression directly to Part 2 of the study, or study termination. The IDMC will be guided by the IDMC Charter.

If the IDMC recommends initiation of the optional Cohort 2, sentinel dosing will be performed in the same way as described above.

For all participants in Cohort 1 and the optional Cohort 2, dosing will occur once a day for a maximum of 14 days or until hospital discharge, whichever occurs earlier.

If the IDMC recommended initiation of the optional Cohort 2, once dosing of all participants in Cohort 2 is completed, the data will be reviewed by the IDMC. The IDMC will advise on the

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conduct of the study, which may include dosing of additional participants in Cohort 2, initiation of Part 2, or study termination.

Section 4.5 provides detailed information on the dosage and drug administration for participants undergoing IMV as well as for those who are extubated.

Participants in Part 1 will have their pre-dose assessments conducted as per the Schedule of Assessments (SoA: Table 1). Study data will be collected as per the SoA until End of Study (EoS). A follow-up call will be performed on Day 28. In addition, a long-term follow-up call will be performed 28 days post final dose (~Day 42). AEs and concomitant medications will be monitored throughout the study period.

Participants in Part 1 who receive less than two doses of study medication while undergoing IMV will be replaced.

3.2 Part 2

The primary objective of Part 2 will be to evaluate the efficacy of SNG001, versus placebo, in participants with a confirmed respiratory virus infection undergoing IMV.

Part 2 will include a total of 550 participants who will receive two syringes of either SNG001 or placebo, in addition to SOC, determined by double-blind randomisation with a ratio of 1:1.

After the first 250 participants have completed all study visits (up to and including Day 28), an interim analysis will be conducted and reviewed by the IDMC. Depending on the outcome of the analysis, the IDMC may recommend for the study to be stopped for futility, or to continue recruitment. If the decision is made for the study to continue, an additional 300 participants will be enrolled.

For all participants in Part 2, daily dosing will occur for a maximum of 14 days or until hospital discharge, whichever occurs earlier.

Section 4.5 provides detailed information on the dosage and drug administration for participants undergoing IMV as well as for those who are extubated.

To ensure participant safety, the IDMC will review safety data from Part 2 once 30 participants and again, once 100 participants have completed study treatment. The IDMC will also meet as and when necessary, i.e., if a safety issue arises or when the IDMC or the Sponsor request a further meeting.

Participants in Part 2 will have their pre-dose assessments conducted as per the SoA (Table 1). Study data will be collected as per the SoA until EoS. A follow-up call will be performed on Day 28. In addition, a long-term follow-up call will be performed 28 days post final dose (~Day 42). AEs and concomitant medications will be monitored throughout the study period.

Participants in Part 2 who receive less than two doses of study medication in the initial 3 days of study treatment may be replaced.

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3.3 Criteria for Inclusion and Exclusion

3.3.1 Part 1

3.3.1.1 Inclusion Criteria

To be eligible for randomisation into Part 1 of the study, each participant must fulfil the following criteria:

1. Informed consent or legal representative's consent obtained.
2. Patients ≥50 years of age at the time of consent.
3. Patient admitted to the ICU and requiring IMV due to a respiratory virus infection.*
4. Presence of Flu A, Flu B, RSV, RV, adenovirus, parainfluenza, HMPV, or coronaviruses (including SARS-COV-2 and seasonal coronaviruses) in a nose swab sample, confirmed by a positive virus test using a Sponsor approved rapid point of care (POC) test (e.g., reverse transcription polymerase chain reaction [RT-PCR]) or SOC test via any sample type (SOC sample collected not more than 48 hours prior to intubation).**
5. Time from intubation to administration of first dose of study medication ≤48 hours.
6. Women of childbearing potential must have a negative pregnancy test. For this study, women of childbearing potential are defined as women <55 years old.

* Patients with confirmed respiratory virus infection and bacterial or fungal respiratory co-infection may be eligible for the study, providing that in the opinion of the Investigator, based on routine clinical, radiological, and microbiological assessments, the primary reason for the patient's ICU admission and IMV is their viral infection.

** The Sponsor will monitor the aetiology of viral infections during the conduct of the study and may decide to limit enrolment of patients with certain viral infections, to achieve a balanced mix of viruses.

3.3.1.2 Exclusion Criteria

A participant must not be randomised into Part 1 of the study if they meet any of the following criteria:

1. Expected termination of IMV within 24 hours from the time of randomisation.
2. Life expectancy <24 hours.
3. Liver failure (Child-Pugh C).
4. Severe congestive heart failure (New York Heart Association [NYHA] IV).
5. Receipt of lung transplant.
6. Known or suspected active tuberculosis, or infection with other mycobacteria.
7. Known or suspected active systemic fungal infection.
8. Anticipated transfer to another hospital, which would prevent the participant from continuing in the study and completing protocol assessments.

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9. Need for long-term mechanical ventilation prior to ICU admission.
10. Use of inhaled sedation.
11. Presence of tracheostomy or laryngectomy.
12. Requirement for airway pressure release ventilation mode.
13. History of hypersensitivity to natural or recombinant IFNβ or to any of the excipients in the drug preparation.
14. Any condition, including findings in the patient's medical history or in the pre-randomisation study assessments that in the opinion of the Investigator, constitute a risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation.
15. Participation in previous clinical studies of SNG001.
16. Current or previous participation in another clinical study where the participant 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.
17. Known or suspected pregnancy.
18. Females who are breast-feeding or lactating.
19. Immunocompromising condition, including:
    a. Established acquired immune deficiency syndrome (AIDS) defined as a cluster of differentiation 4 (CD4) count <200 cells/microL, and/or the presence of any AIDS-defining condition;
    b. Haematological malignancy;
    c. Bone marrow transplantation; or
    d. Immunosuppressive therapy, including:
        - Cancer therapy (e.g. chemo-, radio-, immuno-, hormone or other types of therapy), immune-cell depleting therapy, immunosuppressive therapy for autoimmune disorders, medications for prevention of organ transplantation rejection, administered within 6 months prior to randomisation; or
        - Corticosteroids >20 mg of prednisone or equivalent per day administered continuously for >14 days prior to randomisation.
20. Severe chronic lung disease requiring home oxygen therapy, including chronic obstructive pulmonary disease, asthma, cystic fibrosis, or pulmonary fibrosis.

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3.3.2 Part 2

3.3.2.1 Inclusion Criteria

To be eligible for randomisation into Part 2 of the study, each participant must fulfil the following criteria:

1.a Patients ≥18 and <50 years of age at the time of consent, with an immunocompromising condition, including:

- Solid tumour malignancy undergoing cancer therapy (e.g. chemo-, radio-, immuno-, hormone or other types of therapy);
- Haematological malignancy in remission, with or without maintenance therapy;
- Immunosuppressive therapy for autoimmune disease;
- Therapy for prevention of organ transplant rejection;
- Corticosteroids >20 mg of prednisone or equivalent per day, administered continuously for >14 days prior to randomisation.

or

1.b Patients ≥50 years of age at the time of consent, with or without an immunocompromising condition (as defined above).

2. Patient admitted to the ICU and requiring IMV due to a respiratory virus infection.*
3. Presence of Flu A, Flu B, RSV, RV, adenovirus, parainfluenza, HMPV, or coronaviruses (including SARS-COV-2 and seasonal coronaviruses) in a nose swab sample, confirmed by a positive virus test using a Sponsor approved rapid POC test (e.g., RT-PCR) or SOC test via any sample type (SOC sample collected not more than 48 hours prior to intubation).**
4. Time from intubation to administration of first dose of study medication ≤48 hours.
5. Informed consent or legal representative's consent obtained.
6. Women of childbearing potential must have a negative pregnancy test. For this study, women of childbearing potential are defined as women <55 years old.

* Patients with confirmed respiratory virus infection and bacterial or fungal respiratory co-infection may be eligible for the study, providing that in the opinion of the Investigator, based on routine clinical, radiological, and microbiological assessments, the primary reason for the patient's ICU admission and IMV is their viral infection.

** The Sponsor will monitor the aetiology of viral infections during the conduct of the study and may decide to limit enrolment of patients with certain viral infections, to achieve a balanced mix of viruses.

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3.3.2.2 Exclusion Criteria

A participant must not be randomised into Part 2 of the study if they meet any of the following criteria:

1. Expected termination of IMV within 24 hours from the time of randomisation.
2. Life expectancy <24 hours.
3. Liver failure (Child-Pugh C).
4. Severe congestive heart failure (NYHA IV).
5. Receipt of lung transplant.
6. Known or suspected active tuberculosis, or infection with other mycobacteria.
7. Known or suspected active systemic fungal infection.
8. Immunocompromising condition, including:
    - Haematological malignancy requiring induction or consolidation therapy within 3 months prior to randomisation;
    - Bone marrow transplant within 6 months prior to randomisation;
    - Solid organ transplant within 6 months prior to randomisation;
    - Corticosteroids >75 mg of prednisone or equivalent per day, administered continuously for >7 days prior to randomisation;
    - Methotrexate therapy at randomisation, if the indication is chemotherapy for cancer;
    - Chimeric antigen receptor (CAR)-T cell therapy, administered within 3 months prior to randomisation;
    - Ibrutinib or alemtuzumab, administered within 3 months prior to randomisation;
    - Neutropenia <500/mm^3 not due to sepsis;
    - Clinical presentation consistent with severe bone marrow suppression or pancytopenia;
    - Established AIDS, defined as a CD4 count <200 cells/microL, and/or the presence of any AIDS-defining condition.
9. Anticipated transfer to another hospital, which would prevent the participant from continuing in the study and completing protocol assessments.
10. Need for long-term mechanical ventilation prior to ICU admission.
11. Use of inhaled sedation.
12. Presence of tracheostomy or laryngectomy.
13. History of hypersensitivity to natural or recombinant IFNβ or to any of the excipients in the drug preparation.

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14. Any condition, including findings in the patient's medical history or in the pre-randomisation study assessments that in the opinion of the Investigator, constitute a risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation.
15. Participation in previous clinical studies of SNG001.
16. Current or previous participation in another clinical study where the participant has received a dose of an 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.
17. Known or suspected pregnancy.
18. Females who are breast-feeding or lactating.
19. Severe chronic lung disease requiring home oxygen therapy, including chronic obstructive pulmonary disease, asthma, cystic fibrosis, or pulmonary fibrosis.

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4 STUDY MEDICATION

4.1 Allocation to Study Medication

The study design and Part 2 flow chart are illustrated in Figure 1 and Figure 2, respectively.

Figure 1: Study Design

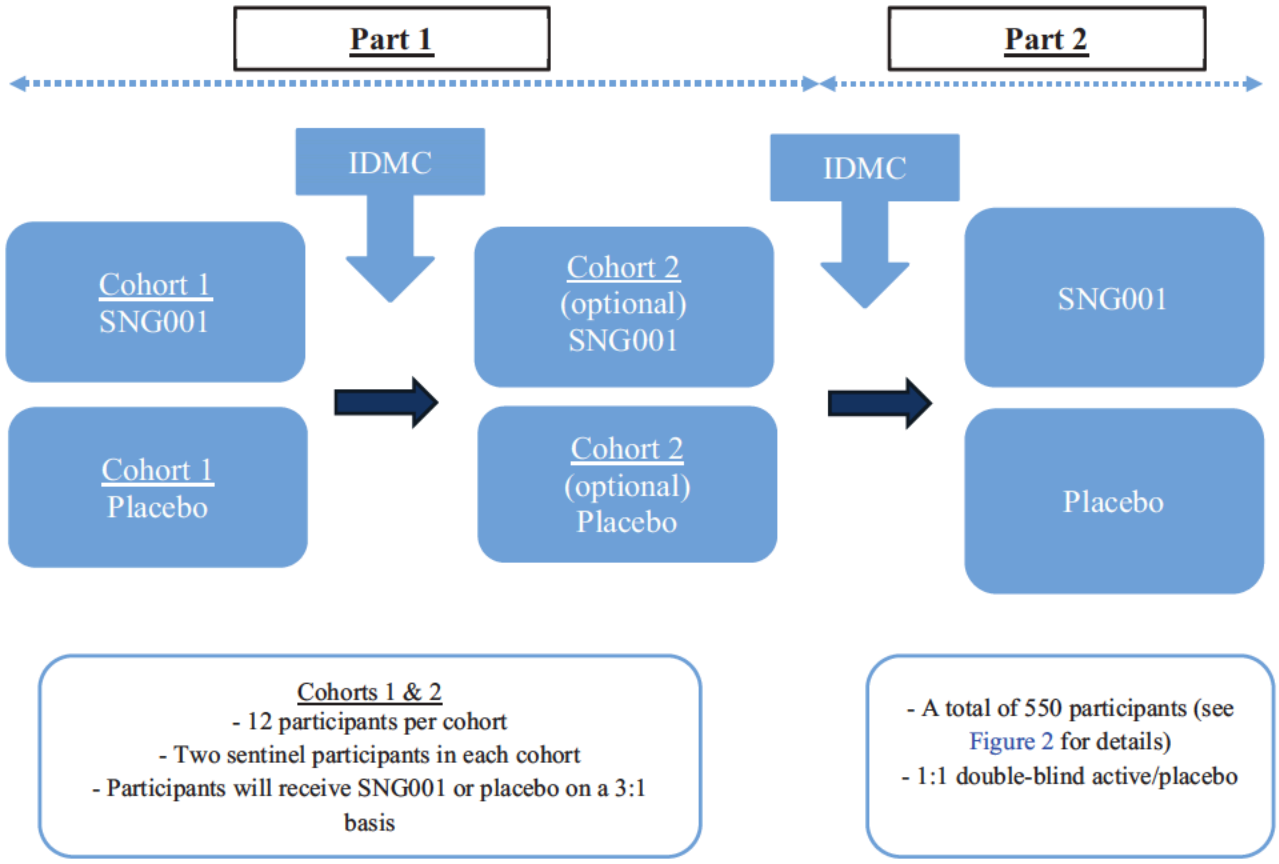
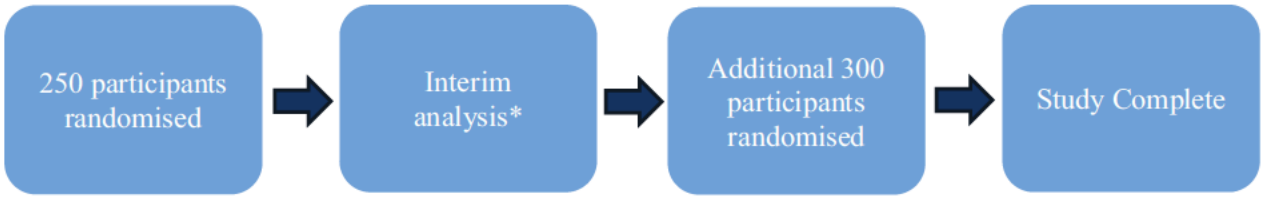


Figure 2: Part 2 Flow Chart



*Study may be stopped for futility at the interim analysis.

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4.1.1 Part 1

Part 1 will include up to two cohorts of 12 participants each. Each cohort will include sentinel dosing of at least two participants, with the remaining participants dosed after safety data for the sentinel participants are evaluated by the SRC. In total, up to 24 participants (excluding participants who were replaced) will receive either SNG001 or placebo, determined by double-blind randomisation with a ratio of 3:1, in addition to SOC, for a maximum of 14 days or until hospital discharge, whichever occurs earlier.

4.1.2 Part 2

Part 2 will include a total of 550 participants (excluding participants who were replaced) who will receive either SNG001 or placebo, determined by double-blind randomisation with a ratio of 1:1. Participants will receive two syringes of either SNG001 or placebo, in addition to SOC, for a maximum of 14 days or until hospital discharge, whichever occurs earlier.

4.2 Breaking the Blind

Both Part 1 and Part 2 of the study will be double-blind. Blinding codes should only be broken in emergency situations for reasons of participant safety. In the event of a need to unblind the participant the Investigator (or delegate) will be able to access the participant treatment allocation information 24 hours a day.

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

4.3 Stopping Rules

4.3.1 Individual Participant Stopping Rules

An individual participant may be discontinued permanently from the study medication for any of the following reasons:

- The participant, or the participant's Legal Representative, withdraws consent for study medication only.
- The participant is experiencing intolerable AEs.
- A protocol deviation has occurred that is deemed by the Investigator to put the participant at increased risk.
- The participant is not capable of receiving the study medication.

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- The Investigator and/or Sponsor feels that it is in the participant's best interest to be withdrawn from the study medication.
- Treatment code prematurely broken by the Investigator.
- Pregnancy.
- Other AEs reflecting a safety concern.
- Other (reason to be specified by the Investigator in the electronic case report form [eCRF]).

An individual participant will be discontinued permanently from the study (i.e., from study medication and data collection) for any one of the following reasons:

- The participant, or participant's Legal Representative, withdraws consent for taking part in the study. If a participant dies after withdrawing consent but within the planned 28-day study period, the date and cause of death will still be reported.
- The participant is lost to follow-up.

4.3.2 Study Stopping Rule

The study may be terminated prematurely for any of the following reasons:

- In the opinion of the Sponsor, SRC, or IDMC, an unacceptable risk to the safety and welfare of participants is posed by the continuation of the study.
- If clinically significant safety concerns arise within this study or in any other study with SNG001 which may impact on the wellbeing of participants in this study.
- If recruitment is slow, at the Sponsor's discretion.
- Other (reason to be specified by the Sponsor).

The study may be terminated prematurely at individual sites for any of the following reasons:

- If the study procedures are not being performed according to the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and cannot be remedied or this is a serious breach.
- If recruitment is slow, at the Sponsor's discretion.
- Other (reason to be specified by the Sponsor).

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

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4.4 Description of Investigational Medicinal Product and Device

The study medication kit number(s) (for SNG001 or placebo) will be assigned by the IRT system at randomisation and the setup of the [redacted] nebuliser is described in the Dosing Manual.

4.4.1 SNG001

The drug substance, recombinant IFNβ-1a, is manufactured under Good Manufacturing Practice conditions.

SNG001 nebuliser solution is presented as a ready-to-use aqueous solution (neutral pH) in glass syringes containing [redacted] of drug product solution containing [redacted] of IFNβ1a.

The filling of the [redacted] nebuliser will depend on the study part and cohort as follows:

- For Part 1, Cohort 1, the [redacted] nebuliser will be filled with the contents of a single syringe of SNG001 ([redacted] of SNG001 solution for inhalation containing [redacted] of IFNβ-1a) equivalent to [redacted] of IFNβ-1a.
- For Part 1, Cohort 2, the [redacted] nebuliser will be filled with the contents of two syringes of SNG001 (each syringe containing [redacted] of SNG001 solution for inhalation [redacted] of IFNβ-1a) equivalent to [redacted] of IFNβ-1a.
- For Part 2, the [redacted] nebuliser will be filled with the contents of two syringes of SNG001 (each syringe containing [redacted] of SNG001 solution for inhalation [redacted] of IFNβ-1a) equivalent to [redacted] of IFNβ-1a.

The IB contains further details of the composition of SNG001 [18].

4.4.2 Placebo

The placebo nebuliser solution is presented in glass syringes containing [redacted] of solution containing the same formulation as the study medication but without IFNβ1a (i.e., only the excipients of the SNG001 solution).

The filling of the [redacted] nebuliser will depend on the study part and cohort as follows:

- For Part 1, Cohort 1, the [redacted] nebuliser will be filled with the contents of a single syringe of placebo.
- For Part 1, Cohort 2, the [redacted] nebuliser will be filled with the contents of two syringes of placebo.
- For Part 2, the [redacted] nebuliser will be filled with the contents of two syringes of placebo.

The IB contains further details of the composition of the placebo [18].

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4.4.3 Inhalation Device

The study medication will be delivered using the [redacted] nebuliser. The [redacted] nebuliser is a portable vibrating mesh nebuliser marketed by [redacted]. In participants undergoing IMV or whose ventilatory support is de-escalated during the course of the study to NIV, the [redacted] nebuliser will be used in combination with [redacted] controller (a controller which detects the breath pattern in a ventilatory circuit and controls aerosol generation). In spontaneously breathing participants who do not require IMV or NIV, the [redacted] nebuliser will be used in combination with [redacted] (a handheld device) and a USB controller, with or without additional oxygen supplementation via LFNC and the [redacted] device oxygen port, is required. Instructions for the use of the [redacted] nebuliser, the [redacted] device, the [redacted] and USB controllers as well as dosing guidance for participants receiving different levels of respiratory support are included in the Dosing Manual. [redacted]

4.5 Dosage and Administration

4.5.1 Dosage

All participants will receive a dose of study medication once a day for a maximum of 14 days or until hospital discharge, whichever occurs earlier.

All participants will take their doses of study medication under the supervision of study staff.

4.5.1.1 Part 1

Part 1 Cohort 1

The [redacted] nebuliser should be filled with the content of a single syringe of SNG001 or placebo.

Part 1 Cohort 2 (Optional)

The [redacted] nebuliser should be filled with two syringes of SNG001 or placebo.

4.5.1.2 Part 2

The [redacted] nebuliser should be filled with two syringes of SNG001 or placebo .

4.5.2 Administration

The study medication should be removed from the fridge for a minimum of 15 minutes prior to administration of the dose and for no longer than 2 hours.

The [redacted] nebuliser may be used in the following settings:

- Whilst the participants undergo IMV, the [redacted] nebuliser will be used under control of the [redacted] to deliver the study medication to the participant via the ventilator circuit.

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- Whilst the participants undergo NIV using Continuous Positive Airway Pressure (CPAP)/Bilevel Positive Airway Pressure (BiPAP) (with a non-vented mask), the [redacted] nebuliser will be used under control of the [redacted] controller to deliver the study medication to the participant via the NIV circuit.

- Spontaneously breathing participants who were de-escalated to lower levels of oxygen supplementation (e.g., non-rebreather, Venturi or simple face masks or low-flow nasal cannula [LFNC]) or who do not require oxygen supplementation will be administered study medication via the [redacted] nebuliser in combination with the [redacted] handheld device under control of the USB controller, while receiving oxygen supplementation via LFNC and the [redacted] device oxygen port, if required.

Administration of study medication during oxygen supplementation using high-flow nasal cannula (HFNC) is not permitted, as it is likely to result in suboptimal doses of study medication being delivered. However, participants receiving oxygen therapy via HFNC may be administered study medication by temporarily changing their respiratory support for the duration of study drug administration to:

- NIV, as described above, or to

- Oxygen supplementation using LFNC (if NIV is not tolerated by the participant) and receiving study medication via the [redacted] nebuliser in combination with the [redacted] device, as described above.

Participants receiving oxygen supplementation using HFNC who cannot tolerate either NIV or LFNC for the duration of study drug administration may need to miss their dose.

Instructions for the use of the [redacted] nebuliser, the [redacted] device, the [redacted] and USB controllers, as well as dosing guidance for participants receiving different levels of respiratory support, are included in the Dosing Manual.

4.5.3 Dose Delivery Times

It is anticipated that a dose of study medication will take approximately 5 to 15 minutes to be delivered, depending on the study medication volume, breathing pattern and/or ventilator mode used.

4.5.4 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.

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4.6 Preparation, Handling, and Dispensing

4.6.1 Preparation Time

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

4.6.2 Timing of Doses

The study medication should be taken once a day at approximately the same time of day.

The study medication should be administered while the participant's respiratory function and level of ventilatory support are stable. If possible, suctioning, postural changes or other standard ICU procedures that have the potential to result in decreased oxygenation levels should be avoided immediately prior to administration of study medication.

4.6.3 Missed or Incomplete Doses

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

1. Record in the source document and the eCRF that the dose has been missed/not completed with the reason why.
2. Continue with any remaining doses as normal (see Section 5.3 for participant withdrawal criteria).

Participants in Part 1 who receive less than two doses of study medication while undergoing IMV will be replaced.

Participants in Part 2 who receive less than two doses of study medication in the initial 3 days of study treatment may be replaced.

4.7 Storage of Study Medication

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

4.8 Drug Accountability

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

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

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Drug accountability records may include:

- Confirmation and inventory of study medication delivery to the study site.
- An inventory of the study medication that has been allocated to each participant.
- Confirmation of administration of each dose of study medication.
- The return to the Sponsor or alternative disposition of unused products.

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

4.9 Treatment of Overdose

An overdose is defined as any dose greater than the once-a-day dose that is being used in this study. Any overdose must be recorded as a protocol deviation.

In the event of overdose, participants should be observed, and symptomatic treatment and monitoring of vital functions should be performed according to routine clinical practice. . The Sponsor (or delegate) should be contacted in an expedient manner, whether associated with an AE (serious or non-serious) or not, to decide if the participant should continue in the study.

5 STUDY PROCEDURES

5.1 Screening Failures

Screening failures are defined as participants for whom informed consent or Legal Representative’s consent have been obtained, but who have not met the study inclusion and/or the exclusion criteria. Participants who are Screening failures will not be re-screened.

5.2 Study Visits

5.2.1 Pre-Treatment (Day -1)

The following assessments should be performed on Day -1* prior to the first dose, preferably in the following order:

- Informed consent.
- Inclusion/exclusion criteria.
- Nose swab sample for rapid POC viral load testing to confirm patient’s eligibility. Alternatively, a SOC test on a sample (any sample type) collected not more than 48 hours prior to intubation can be used to confirm eligibility.

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- Tracheal aspirate sample for rapid POC viral load testing (to be performed at all sites, study Part 1 and Part 2). For study Part 1 and Part 2 at selected sites only, this sample will also be processed and frozen samples will be sent to the central laboratory.
- Participant demographics.
- Urine pregnancy test, if applicable.
- Medical history.
- Physical examination.
- Height and weight (actual or estimated, could be taken from medical records, if available).
- Vital signs (to include temperature and other vital signs, as required for calculation of APACHE II and mSOFA score).
- Acute Physiology and Chronic Health Evaluation II (APACHE II) score.
- mSOFA score.
- Randomisation.
- OSCI.
- Ventilatory and oxygenation support parameters, including partial pressure of oxygen in arterial blood (PaO_2) to the fraction of inspiratory oxygen concentration (FiO_2) ratio (PaO_2/FiO_2 ratio), or oxygen saturation (SpO_2) to FiO_2 ratio (SpO_2/FiO_2 ratio), as applicable.
- AEs, SAEs, and concomitant medications (from the time informed consent was signed).

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

* For patients in ICU, who are assessed to have capacity and are consented to the study prior to the commencement of IMV, Day-1 will be the day IMV begins.

5.2.2 Day 1

The following assessments should be performed on Day 1, prior to dose administration, preferably in the following order:

- Vital signs (to include temperature and other vital signs, as required for calculation of mSOFA score).
- Physical examination.
- Ventilatory and oxygenation support parameters, including PaO_2/FiO_2 ratio or SpO_2/FiO_2 ratio, as applicable.
- Tracheal aspirate sample for rapid POC viral load testing (all sites, study Part 2 only, to be performed at the study site) and sample processing (to be performed by selected sites only, study Part 1 and Part 2 and frozen samples to be sent to central laboratory).
- Serum sample for biomarkers and AAbs.

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- PAXgene DNA blood sample.
- PAXgene RNA blood sample.
- mSOFA score.
- OSCI.
- AEs, SAEs, and concomitant medications.

When assessments have been performed, study medication will be administered.

Participants may receive the first dose of study medication either on the same day as the pre-treatment assessments or the next day, depending on timings. If Day -1 and Day 1 assessments are performed on the same day, the assessments required for both days only need to be performed once.

5.2.3 Days 2 to 14

Participants who previously lacked capacity, should be assessed for regained capacity prior to assessments being performed. Informed consent should be re-obtained from the participant once capacity is regained between Day 2 to Day 14.

Unless stated otherwise, the following assessments should be performed daily from Day 2 to 14, prior to dose administration, preferably in the following order:

- Vital signs (to include temperature and other vital signs, as required for calculation of mSOFA score).
- Physical examination, as clinically indicated.
- Ventilatory and oxygenation support parameters, including PaO_2/FiO_2 ratio or SpO_2/FiO_2 ratio, as applicable.
- Tracheal aspirate samples for rapid POC viral load testing (all sites, study Part 2 only) and sample processing with frozen samples to be sent to central laboratory (selected sites only, study Part 1 and Part 2). Sample collection to be performed daily (one sample per day), pre-dose while the participant is undergoing IMV or until Day 7, whichever is earlier. For participants in Part 2 who undergo IMV for longer than 7 days sample collection for rapid POC viral load testing only (to be performed by all sites) should also be performed on the last day of IMV or on Day 14, whichever is earlier.
- Serum sample for biomarkers (once a day, pre-dose up to Day 7).
- PAXgene RNA blood sample (once a day, pre-dose up to Day 7).
- mSOFA score (daily while the participant is in the ICU).
- OSCI.
- AEs, SAEs, and concomitant medications.

When assessments have been performed, study medication will be administered.

If the participant has discontinued dosing and consents to data collection, attempts should be made to collect the following key data (see also Section 5.3 and 5.4 for further details):

- OSCI.
- Recording of AEs, SAEs, and concomitant medications.

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5.2.4 End of Treatment (within 24 hours post last dose)

These assessments should be performed in hospital within 24 hours post last dose. For participants that are being discharged from hospital, this visit should occur in hospital prior to discharge (see Sections 4.3.1 and 5.3). Participants who previously lacked capacity, should be assessed for regained capacity prior to assessments being performed. Informed consent should be re-obtained from the participant if capacity is regained at the End of Treatment visit.

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

- Vital signs (to include temperature and other vital signs, as required for calculation of mSOFA score.
- Physical examination, as clinically indicated.
- Ventilatory and oxygenation support parameters, including PaO_2/FiO_2 ratio or SpO_2/FiO_2 ratio, as applicable.
- mSOFA score (if the participant is still in the ICU).
- OSCI.
- Recording of AEs, SAEs, and concomitant medications.

If the participant has discontinued dosing and consents to data collection, attempts should be made to collect the above data (see also Sections 5.3 and 5.4 for further details).

5.2.5 Follow-up (Day 28 [+2 days])

A follow-up assessment will be performed, either face-to-face if the participant remains in hospital or via telephone/video call if the participant has been discharged from hospital, to record:

- OSCI for participants who remain hospitalised.
- AEs and SAEs, including pre-specified respiratory and cardiovascular deteriorations, as per Sections 7.6.1 and 7.6.2.
- Duration of ICU and hospital stay and survival status.
- Need for organ support

If site staff are unable to contact the participant on Day 28, every effort should be made to contact the participant and request the participant undergoes the follow-up regarding any unresolved AEs.

For participants that continue to lack capacity at this visit, the research site staff conducting this visit should assess the participant's capacity at the beginning of the visit. Informed consent should be re-obtained from the participant if capacity is regained at the Follow-up visit. If the participant continues to lack capacity, attempts should be made to contact the Legal Representative to collect the Day 28 data. If it is not possible to contact the Legal Representative,

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survival status should be recorded from the medical records; however, it may not be possible to collect other Day 28 data (i.e., details regarding ongoing AEs and SAEs).

If the participant has discontinued dosing and consents to data collection, attempts should be made to collect the above data (see also Sections 5.3 and 5.4 for further details).

5.2.6 Long-term Follow-up (Day 42 [28 days post final dose +2 days])

A Long-term Follow-up assessment will be performed, either face-to-face if the participant remains in hospital or via telephone/video call if the participant has been discharged from the hospital, to record participants survival status, need for organ support and status of ongoing AEs or SAEs, as per Sections 7.6.1 and 7.6.2.

If site staff are unable to contact the participant on Day 42, continued attempts should be made via telephone/video call twice a week for at least 2 weeks.

For participants that continue to lack capacity at this visit, the research site staff conducting this visit should assess the participant's capacity at the beginning of the visit. Informed consent should be re-obtained from the participant if capacity is regained at the Long-term Follow-up assessment. If the participant continues to lack capacity, attempts should be made to contact the Legal Representative and if this is not possible, the data should not be collected.

5.3 Participant/Legal Representative Withdrawal

Participants or Legal Representatives may withdraw from the study at any time.

If the participant/Legal Representative withdraws from study participation, the Sponsor will retain and continue to use any data collected before such a withdrawal of consent. If the participant regains capacity and does not give consent to continue in the study, the Legal Representative consent remains for all data/sample collected up to the point where the participant has regained capacity and declined the study.

If the participant is withdrawn from the study or from the study medication, the reason for withdrawal will be documented in the source documents and eCRF. Discontinuation of study medication does not represent withdrawal from the study and the study schedule should be followed until Day 42 Long-term Follow-up assessment.

If the participant/Legal Representative withdraws from the study, the following options should be discussed with the participant/Legal Representative:

Option 1:

Consent withdrawn for further participation in the study but remains for sample analysis for study purposes and subsequent analysis where samples have been gifted.*

Option 2:

Consent withdrawn for further participation in the study and for the gifting of samples but consent remains for sample analysis for study purposes.*

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Option 3:

Consent withdrawn for all further participation in the study including all sample analysis.

Samples collected but not analysed will be destroyed. Partially completed sample analysis will be stopped and the sample data withdrawn. Any remaining samples will be destroyed when consent is withdrawn. It will not be possible to remove any data which has already been included in combined analysis at the point of consent withdrawal.*

* If a participant/Legal Representative withdraws consent with either option 1, 2, or 3, consent should be requested by the research team to collect Day 28 survival status from the medical records. This consent should be documented in the source documents.

5.4 Lost to Follow-up

Participants (who have been assessed as having regained capacity) will not be considered as lost to follow-up if no contact is made with the participant at the Day 28 Follow-up assessment or Day 42 Long-term Follow-up assessment.

If a participant does not respond to the Day 28 Follow-up assessment, every effort should be made to contact the participant and request the participant undergoes the follow-up regarding any unresolved AEs. Please refer to Section 4.3.1 for individual participant stopping rules. If no contact is made, survival status should be collected from the medical records and the site should continue with the scheduled Day 42 Long-term Follow-up assessment.

If a participant does not respond to the Day 42 Long-term follow-up assessment, the site should make every effort to contact the participant, twice a week for at least 2 weeks. A participant will only be considered as ‘lost to follow-up’ if no contact is re-established following all attempts.

The status of ‘lost to follow-up' should be amended in the eCRF if participant contact is re-established and additional study follow-up data can be obtained.

If the participant continues to lack capacity, attempts should be made to contact the Legal Representative. If no contact is made, the steps outlined above for Days 28 and 42 assessments should be followed for the Legal Representative.

6 STUDY PROCEDURES AND ASSESSMENTS

6.1 Informed Consent

Informed consent will be obtained prior to any study procedures being performed. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH GCP, and all applicable laws and regulations for each country. A clinically qualified, delegated member of the study team, i.e., a medical doctor or a qualified nurse, can obtain informed consent.

It is not expected that many patients considered for enrolment in the study will have the capacity to consent to take part at the time of enrolment, due to the nature of the underlying disease, as

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they will be under sedation and will be mechanically ventilated. Consent to participate in the study will be obtained from a Legal Representative (personal or professional).

ICU patients with a suspected viral infection, not yet undergoing IMV, and who are deemed to have capacity, can be approached for the study using the Patient Information Sheet and Informed Consent form.

Each site should follow their country and local guidance on Legal Representatives.

The Legal Representative will be fully informed of all aspects of the study and the potential risks. The following will be emphasised in relation to the patient:

- Participation in the study is entirely voluntary.
- Refusal to participate involves no penalty or loss of medical benefits.
- The participant/Legal Representative may withdraw from the study at any time resulting in no detriment to care or treatment for the participant.
- The Legal Representative is free to ask questions at any time to allow them to understand the purpose of the study and the procedures involved.
- There may be no direct benefit from the patient's participation.
- The aims of the study and all tests to be carried out will be explained. The Legal Representative will be given the opportunity to ask about details of the study and will then have time to consider whether they wish for the patient to participate or not.
- The risks of participating in the study will be fully explained.
- Any advance decisions/wishes regarding participation in research made by the participant that the Legal Representative is aware of should be respected.

If the Legal Representative decides that they wish for the patient to participate, they can sign and date the Legal Representative Consent Form. The original copy will be stored as source documentation and a copy is to be given to the Legal Representative.

The method of obtaining consent may vary due to the nature of this study. Different methods, including written, verbal (via telephone) or electronic consent may be used. Whichever method is used informed consent will always be obtained from a Legal Representative prior to any study related procedures being performed.

However consent is obtained, the process should be documented in the participant's source notes.

The Legal Representative will be given sufficient time to review the information provided and ask questions before signing the Consent Form.

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Enrolled participants regaining capacity

Once participants have regained capacity, they will be asked to consent to their continued participation in the study. The study rationale and conduct will be explained to them outlining any interventions which have already been undertaken as well as those that are still required. Information concerning the Legal Representative consent process already completed on the participant's behalf whilst they were incapacitated will also be provided. Details of the informed consent discussion will be recorded in the participant's medical record. This will include the date consent was given, with the name of the study and the version number of the participant information sheet and informed consent form (ICF). The original ICF will be stored as source documentation, a copy will be given to the participant and a copy also placed in the medical and study notes. Participants who decline consent at this time will be withdrawn from the study as detailed in Section 5.3.

Throughout the study the participant or Legal Representative should have the opportunity to ask questions about the study, and any new information that may be relevant to the participant's continued participation should be shared with them in a timely fashion. On occasion, it may be necessary to re-consent the participant or Legal Representative, for example if new information becomes available or an amendment is made to the protocol that might affect the participant's participation in the study. In this case the process above will be followed and the patient's right to withdraw from the study respected.

The participant or Legal Representative will be asked to consent for the use of their/the participants samples in future research, if any sample is left over once all planned analyses have been performed. Any samples stored for future research will be anonymised. Consent for this is optional. If the participant/Legal Representative chooses not to consent, any remaining samples will be destroyed. See Section 5.3 for details regarding withdrawal of consent.

6.2 Medical and Viral Infection History

The participant's medical history and details of the current respiratory infection will be recorded in the source documents by the Investigator or their delegate on Day -1 after informed consent has been obtained. This information will be gained from the participant's hospital medical records and will ensure the participant's eligibility.

6.3 Participant Demography

Information regarding participant's demographics can be obtained from the participant's medical records after informed consent has been obtained. These will include age, sex, and race/ethnicity, unless local laws or regulations do not permit this.

6.4 Physical Examination

A physical examination will be performed on Day -1 or Day 1 prior to the first dose as per the SoA (Table 1).

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

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The need for and the extent of the examinations will vary from participant to participant, and will depend on the clinical circumstances, as deemed by the investigator.

Once a participant has moved out of the ICU, details of physical examination taken as SOC can be used from the medical records.

Results of the examinations will be recorded in the source documents.

6.5 Height and Weight

Height and weight (actual or estimated) will be recorded on Day -1, after informed consent has been obtained (could be taken from medical records, if available).

6.6 Vital Signs

Vital signs include temperature and other vital signs, as required for calculation of APACHE II and mSOFA scores.

The highest temperature measurement each day should be reported.

6.7 Ordinal Scale for Clinical Improvement

As the study will not assess participants' limitation of activity and clinical or virological evidence of infection post hospital discharge, the OSCI to be used in this study is an adaptation of the 18 February 2020 World Health Organization version [20].

Table 2: Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Ambulatory	Patient discharged	2
Hospitalised	Hospitalised, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalised	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Abbreviations: RRT: renal replacement therapy; ECMO: extracorporeal membrane oxygenation

The assessment should be carried out once a day from Pre-treatment Day -1 until Day 14 or until discharge (whichever is sooner) and should reflect the highest level of respiratory support (if any) administered during the day. For participants who remain hospitalised on Day 28 the assessment should also be carried out on Day 28. It is recommended that this assessment should be carried out by a clinically qualified member of the study team, i.e., a medical doctor or a qualified nurse.

The participant's status on the day of hospital discharge should be assessed as ambulatory (OSCI score of 2).

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6.8 Ventilatory and Oxygenation Support

Details of ventilatory and oxygenation support will be recorded in the eCRF, including:

- Selected modes and settings of IMV.
- Use of ECMO.
- Mode of NIV (i.e., CPAP/BiPAP).
- Other oxygenation support (i.e., high-flow [HFNC] and low-flow [LFNC or face mask] oxygen therapy).
- Inspired fraction of oxygen administered and PaO_2/FiO_2 ratio or SpO_2/FiO_2 ratio, as applicable:
    - PaO_2/FiO_2 ratio to be collected whilst the participant is intubated and undergoing IMV, unless an arterial blood sample cannot be collected.
    - SpO_2/FiO_2 ratio to be collected once the participant has been extubated and is receiving respiratory support using NIV or oxygen supplementation using HFNC, face mask or LFNC, and in circumstances where a participant is undergoing IMV, but an arterial blood sample cannot be collected.

Ventilatory and oxygenation support modes (e.g. ECMO, IMV, NIV, HFNC, LFNC, etc) should be recorded as the highest level of respiratory support administered during the day.

Ventilatory and oxygenation support parameters (e.g. PaO_2/FiO_2 or SpO_2/FiO_2 ratio, mean airway pressure, positive end-expiratory pressure, peak inspiratory pressure, tidal volume, etc) should be assessed when the participant's respiratory function and level of respiratory support is stable, prior to the administration of the study medication and before collection of the tracheal aspirate sample.

Intubation and extubation dates, as well as date of tracheostomy (if applicable) should be recorded in the eCRF.

6.9 Oxygenation Index

The severity of hypoxic respiratory failure will be assessed using the Oxygenation Index [Oxygenation Index = (mean airway pressure × FiO_2 × 100)/PaO_2] once a day. The index will be calculated using the relevant ventilatory and oxygenation parameters captured in the eCRF. On Pre-treatment Day -1 the parameters should be recorded when the participant's respiratory function and level of ventilatory support are stable. On Day 1 to Day 4, they should be measured prior to dosing whilst the participant is undergoing IMV.

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6.10 APACHE II Score

The severity of the participant's illness will be assessed by the APACHE II score on Day -1. The score will be calculated using the worst value for each variable in the 24 hours prior to Day -1. Details of the APACHE II score are provided in Appendix A.

6.11 Modified SOFA Score

Five-component mSOFA score (excluding the neurological sub-score) will be calculated once a day from Pre-treatment Day -1, whilst the participant is in the ICU. The respiratory and cardiovascular sub-scores should be assessed when the participant's respiratory and cardiovascular function is stable, prior to the administration of the study medication and before collection of the tracheal aspirate sample. The liver, coagulation and kidney sub-scores should be assessed using routine laboratory test results obtained on the same calendar day. Details of the mSOFA score are provided in Appendix B.

6.12 Organ support

Assessment of organ support, including the use of ventilation, oxygen supplementation, renal replacement therapy, cardiovascular system support including vasopressors and inotropes, ECMO or liver support should be performed at 28 days from randomisation and at 28 days post final dose.

6.13 Laboratory Assessments

6.13.1 Nose swab sample

A nose swab sample will be collected and used for rapid POC viral load testing to confirm patient eligibility for the study. Alternatively, a SOC test on a sample (any sample type) collected not more than 48 hours prior to intubation can be used to confirm eligibility.

6.13.2 Tracheal Aspirate Sample

A tracheal aspirate sample with a 10 mL saline flush will be collected and analysed as follows:

- On Day -1 a single sample will be collected and used for rapid POC viral load testing (all sites, study Part 1 and Part 2). After use for viral load testing, the tracheal aspirate sample will be processed, and frozen samples to be sent to central laboratory (selected sites only, study Part 1 and Part 2).

- From Day 1 for as long as the participant is undergoing IMV or until Day 7, whichever is earlier, a sample will be taken once a day, pre-dose for rapid POC viral load testing (to be performed by all sites, study Part 2 only) and sample processing (to be performed at selected sites only, study Part 1 and Part 2 and frozen samples to be sent to central laboratory).

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- For participants who undergo IMV for longer than 7 days, sample collection for rapid POC viral load testing only (to be performed by all sites, study Part 2 only) should also be performed on the last day of IMV or on Day 14, whichever is earlier.

6.13.3 Serum Sample for Biomarkers and AAbs

A serum sample for IFNβ-dependent and disease relevant biomarkers and AAbs should be taken pre-dose once a day at approximately the same time each day from Day 1 until Day 7 (AAbs will be measured at Day 1 only).

6.13.4 PAXgene Blood Samples for Biomarkers

A PAXgene DNA blood sample should be collected pre-dose on Day 1 to investigate links between genetics, treatment, and participant outcome.

A PAXgene RNA blood sample for biomarkers should be taken pre-dose once a day at approximately the same time each day from Day 1 until Day 7.

6.13.5 Urine Pregnancy Test (If Applicable)

Early detection pregnancy strips (minimum detection 10 MIU human chorionic gonadotrophin) will be used on Day -1.

Urine pregnancy testing is not required for women who are not of child-bearing potential. For this study, women not of childbearing potential are defined as women ≥55 years old.

6.13.6 Recording of Co-infections

Assessment of bacterial, viral and/or fungal co-infections should be performed as per SOC procedures. All confirmed co-infections should be recorded in the eCRF.

6.14 Concomitant Medications

Concomitant medications administered whilst the participant is hospitalised will be recorded in the eCRF. However, there is no requirement to record routine medications common to all critically ill patients such as sedations, analgesia, neuromuscular blockade, bowel care medications, gastric protective medications, thromboembolism prophylaxis, nasogastric tube feeding or intravenous fluids. This information will be available in participants' medical records.

Concomitant medications administered to treat or prevent viral, fungal, or bacterial infections as well as all medications administered via inhaled route should be recorded in the eCRF. The dosage, dates of administration, and reasons for use will be recorded.

Concomitant medications administered to treat AEs should be recorded in the eCRF.

If possible, administration of any inhaled medications should be avoided within 2 hours prior to and after administration of study medication.

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No SOC concomitant medications, including antiviral treatments, will be withheld because of participation in this study.

6.15 Prohibited Medications

The risk of PK drug-drug interactions after inhaled IFNβ-1a administration is expected to be negligible due to low observed systemic exposure. However, as no formal drug interaction studies for SNG001 have been performed in humans and IFNs have been reported to reduce the activity of hepatic cytochrome P450 dependent enzymes, caution should be exercised with participants 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).

Concomitant administration of study medication and inhaled sedation is not allowed. Patients who require administration of inhaled sedation should not be enrolled into the study. Participants who require inhaled sedation during the study should have their study medication discontinued for the duration of inhaled sedation.

6.16 Co-Enrolment into Additional Studies

As detailed in the exclusion criteria, current or previous participation in another clinical study where the participant has received a dose of an 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 is not allowed.

Co-enrolment into other interventional studies (not using an IMP) as well as observational studies during the treatment and follow-up phases up to Day 28 may be acceptable, providing it does not interfere with study assessments. Co-enrolment into any such study must be discussed with the Medical Monitor to clarify whether co-enrolment is permitted.

7 ADVERSE EVENT REPORTING

7.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study participant 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 apparently unrelated illnesses, including the worsening of a pre-existing illness, injury, or accident.

Due to the severity of disease of the study participants, numerous clinical issues, signs, and symptoms will occur during the course of the study that can be deemed expected critical care events (e.g., skin abrasion and pressure ulcers, venipuncture/arterial puncture bruising and infection, variations of core body temperature, temporary reduction in urine output, fluctuations in respiratory and cardiovascular variables, minor deviations of laboratory values outside of normal range, etc). Such expected critical care events will not necessarily constitute a reportable

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AE and should only be reported if they require significant intervention, are considered by the Investigator to be associated with the study medication, lead to discontinuation of study medication, or are otherwise considered to be of concern in the Investigator's clinical judgement.

Specifically, the following guidance should be followed when reporting AEs related to the respiratory virus infection under study:

- Events that should not be reported as an AE:
    - Respiratory virus infection present at study entry.
    - Individual signs and symptoms related to confirmed respiratory virus infection present at study entry.
    - Worsening of signs and symptoms related to the confirmed respiratory virus infection, unless, in the Investigators' opinion, the signs or symptoms are clinically significant or lead to treatment.
- Events that should be reported as an AE:
    - New signs and symptoms related to the confirmed respiratory virus infection that start after the initiation of study treatment.
    - New or worsening signs and symptoms related to the confirmed respiratory virus infection that prolong the participant's anticipated ICU and/or hospital stay.
    - Bacterial, viral or fungal co-infections that, in the Investigator's opinion, are clinically significant or lead to treatment.

The following respiratory and cardiovascular deteriorations occurring during the study should be reported as AEs:

- Acute and sustained hypoxemia (i.e., lasting at least 1 hour) in the first 2 hours post dose defined as:
    - An increase in the fraction of inspired oxygen (FiO_2) of 0.2 or more, or an increase in positive end-expiratory pressure of more than 5 cm H_2O required to maintain the peripheral oxygen saturation within the target range for the participant.

      Reportable increases in FiO_2 or positive end-expiratory pressure should not be related to routine tracheal suctioning manoeuvre, participant's postural changes, or other standard ICU procedures that are known to result in decreased oxygenation levels. Such procedures should be avoided within 2 hours after administration of study medication.
- Acute and sustained hypotension (i.e., lasting at least 1 hour) in the first 2 hours post dose defined as mean arterial pressure decrease of more than 20%, despite titration of inotropes/vasoconstrictors.

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- Acute rise in peak inspiratory airway pressure of more than 10 cm H_2O occurring within the first 2 hours post dose required to maintain tidal volume in the participant's target range and/or acute decrease in tidal volume of more than 30% occurring within the first 2 hours post dose.

- Acute bronchospasm: in the first 2 hours post dose.

- New pulmonary embolism/pneumothorax.

In clinical studies conducted in the ICU, deviations, e.g., in laboratory values or temporary changes in arterial blood pressure, are to be expected frequently. Investigator judgement should be applied in determining which clinical deviations should be reported as an AE in the sense of an "untoward medical occurrence" and which deviations should be considered usual and expected findings in this setting. It is preferred to report the condition or disease underlying the aberrant laboratory value (e.g., 'renal failure') rather than the laboratory value only (e.g., 'hyperkalaemia').

Similarly, it is preferred to report the underlying condition rather than the resulting sign (e.g., 'agitation' rather than 'self-extubation').

The terms 'disease progression', 'progressive disease', or similar, do not constitute an acceptable description of the nature of an AE.

Care will be taken not to introduce bias when detecting AEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

If a participant 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, to obtain all information necessary to facilitate appropriate reporting of the event.

7.2 Serious Adverse Events

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.

Or

- Other medically important condition.

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 participant 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.

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Re-intubation or re-admission to ICU must be reported as an SAE.

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

7.3 Assessment of Adverse Events

The Investigator will assess every AE to determine if it is serious or not (see Section 7.2 for definition criteria). This assessment will determine the reporting procedures to be followed.

7.3.1 Relationship to Study Medication

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

7.3.1.1 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 participant'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 [18] 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,

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	concomitant medication more likely associated with the event) or a convincing alternative explanation for the event.
Unrelated:	A causal relationship is not reasonably related in time to the administration of the study medication, or exposure to the study medication has not occurred.

7.3.1.2 Severity

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

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

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

7.4 Discontinuation of Study Medication Due to an AE

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

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

7.5 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 participant becomes pregnant during the conduct of the study, study medication will be discontinued immediately, and the Sponsor (or delegate) should be notified within 24 hours using the Pregnancy Report Form. Follow-up information regarding the outcome of the pregnancy and any foetal or neonatal sequelae should be obtained and documented. For all pregnant participants, 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 participant and the unborn baby until the pregnancy comes to term and the outcome of the

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pregnancy is recorded. If the participant refuses this monitoring, they will be asked to inform study staff about the outcome of the pregnancy.

7.6 Adverse Events Recording and Reporting

7.6.1 Reporting of Adverse Events

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

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

7.6.2 Recording of Adverse Events

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

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study participant 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.

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

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

Resolution means:

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

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

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

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

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

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

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

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8 DATA ANALYSIS/STATISTICAL METHODS

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

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

8.1 Sample Size Determination

8.1.1 Part 1

Cohort 1 and the optional Cohort 2 will enrol 12 participants each.

8.1.2 Part 2

A sample size of 550 participants provides more than [redacted] power to detect an RRR in mortality of [redacted]. This sample size has been calculated using a 1-sided 2.5% alpha level of superiority and assumes that [redacted] of participants randomised to placebo will die within 28 days. All deaths within 28 days of randomisation are expected to be recorded in the eCRF. Therefore, no adjustment for participant drop-out has been used.

This sample size allows for an interim analysis of the first 250 randomised participants for futility. Further details of the planned interim analysis are provided in Section 8.8.

Prior to unblinding for the interim analysis, the blinded event rate will be assessed, and the sample size may be increased to ensure the final analysis is adequately powered.

8.2 Randomisation

Participants enrolled into Part 1 will be randomised 3:1 to SNG001 or placebo, with 1:1 sentinel dosing for at least the first 2 participants in each cohort.

Participants enrolled into Part 2 will be randomised 1:1 to SNG001 or placebo. Randomisation for Part 2 will be stratified by site and age group/immunocompromising condition status. Age group/immunocompromising condition status will fall into one of the following 3 categories:

- Aged ≥18 and <50 years of age at the time of consent and with an immunocompromising condition,
- Aged ≥50 years of age at the time of consent and without an immunocompromising condition,
- Aged ≥50 years of age at the time of consent and with an immunocompromising condition.

Immunocompromising conditions are defined in Section 3.3.2.1.

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Screened participants will be allocated a unique eight-digit participant identification number. Identification numbers will be assigned sequentially to each participant within each site and will identify the participant throughout the study.

8.3 Analysis Sets

The enrolled set is defined as all participants for whom informed consent has been obtained.

- The Part 1 enrolled set is defined as all participants in the enrolled set who were enrolled onto Part 1 of the study.
- The Part 2 enrolled set is defined as all participants in the enrolled set who were enrolled onto Part 2 of the study.

The intent-to-treat set is defined as all randomised participants.

The modified intent-to-treat (mITT) set is defined as all randomised participants who receive at least two doses of study medication in the initial 3 days of study treatment.

The per protocol set is defined as all participants in the mITT set who do not have any protocol deviations with an impact on efficacy.

The safety set is defined as all participants who receive at least one dose of study medication.

- The Part 1 safety set is defined as all participants in the safety set who were enrolled onto Part 1 of the study.
    - The dose escalation set is defined as all participants in the Part 1 safety set who receive at least two doses of study medication while receiving IMV.
- The Part 2 safety set is defined as all participants in the safety set who were enrolled onto Part 2 of the study.

Additional analysis sets may be defined in the SAP to support the analyses for the populations defined in the estimands.

8.4 Statistical Analysis Methodology for Efficacy Endpoints

The primary objective of this clinical study translates into the following hypothesis:

$$H0: RRR \leq 0$$
$$H1: RRR > 0$$

A SAP will be completed prior to the interim analysis.

All collected data will be summarised using descriptive statistics. Summary statistics will consist of the number of observations, mean, standard deviation, minimum, median, and maximum for continuous parameters, and number and percent of participants for categorical parameters.

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Changes respective to Baseline will also be evaluated where applicable. Baseline is defined as the last assessment prior to first dose.

Part 1 results will be summarised only, and therefore no specific estimands have been defined. Estimands are for Part 2 of the study are defined in Section 2.2.

8.4.1 Analysis of the Primary Efficacy Endpoint

All-cause mortality within 28 days from randomisation will be analysed on the mITT set using a logistic regression model with fixed effects for treatment group, site/region, virus with a positive test at enrolment, and age/immunocompromising condition status. The observed proportion of primary endpoint events will be summarised alongside the adjusted RRR, adjusted proportions, difference in adjusted proportions, and the odds ratio. If analytical issues occur due to quasi-complete or complete separation, a Firth Logistic regression model will be used.

Supportive supplementary estimands for the primary estimand will be defined in the SAP.

8.4.2 Analysis of Secondary Efficacy Endpoints

Change from baseline in average mSOFA score will be analysed as the average change from baseline in mSOFA score both over the first 5 days after randomisation and over the entire ICU stay or until death or Day 14, if still in ICU, whichever occurs first. An analysis of covariance (ANCOVA) with fixed effects for treatment group, site/region, virus, and age/immunocompromising condition status, and a covariate for baseline mSOFA score will be utilised. Missing mSOFA scores over the assessment period will not be imputed.

Time to extubation, duration of ICU stay, and duration of hospital stay will be analysed using a Cox Proportional Hazards model with fixed effects for treatment group, site/region, virus, and age/immunocompromising condition status. Ties in event times will be handled using the exact method, or the Efron approximation if computational difficulties arise. The hazard ratio for SNG001 versus placebo will be presented. Kaplan-Meier estimates of quartiles will also be presented.

All-cause mortality within 28 days post final dose and alive and free of organ support at 28 days from randomisation and at 28 days post final dose will be handled using similar methods to the primary analysis.

Participants who withdraw from the study prior to the occurrence of the event will be censored at the date of withdrawal. Participants who have not experienced the event at the end of the follow -up period will be censored at the date of last contact. Participants who die prior to the event will be censored at the maximum follow-up time + 1 day.

Ventilator-free days will be assessed using an ordered logistic regression using a proportional odds assumption with fixed effects for treatment group, site/region, virus, and age/immunocompromising condition status. The number of ventilator-free days will be calculated as 28 minus the number of days between randomisation and extubation. Participants

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extubated and re-intubated within 48 hours will not be considered ventilator-free on those days. Participants on a ventilator for 4 days or fewer will be grouped together, to give a maximum score of 24 days. Participants who are on a ventilator 28 days after randomisation will therefore be assigned a score of 0. Participants who die within 28 days of randomisation will be assigned a score of -1. Participants who withdraw after extubation will be assumed to be off ventilator until 28 days after ventilation. Participants who withdraw prior to extubation will be excluded from the analysis. Odds ratios for the increase in one ventilator-free day will be presented.

Change in OSCI score, will be analysed using an ordered logistic regression using a proportional odds assumption with fixed effects for treatment group, site/region, virus, and baseline OSCI score. Odds ratios for a better outcome will be presented.

Time to first negative virus test will be analysed using a Cox Proportional Hazards model with fixed effects for treatment group, site/region, virus, and age/immunocompromising condition status. Ties in event times will be handled using the exact method, or the Efron approximation if computational difficulties arise. The hazard ratio for SNG001 versus placebo will be presented. Kaplan-Meier estimates of quartiles will also be presented.

Supportive supplementary estimands for the secondary estimands will be defined in the SAP.

8.4.3 Analysis of Exploratory Efficacy Endpoints

[redacted]

8.4.4 Handling of Missing Data

For the analysis of the primary estimand, all deaths within 28 days are expected to be recorded in the eCRF regardless of participant withdrawal. Therefore, no imputation of deaths will be performed post withdrawal.

Further details regarding missing data approaches, including details of missing data imputation for the secondary estimands will be given in the SAP.

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8.5 Safety Analysis

The secondary safety estimand will be evaluated primarily on AE/SAE information which will be summarised descriptively, including a summary of treatment-emergent AEs/SAEs. AEs/SAEs will be summarised by Medical Dictionary for Regulatory Activities preferred term and system organ class. Summaries by severity, seriousness, and drug-relatedness will also be presented. All SAEs and Suspected Unexpected Serious Adverse Reactions will be summarised according to seriousness categorisation, number, event preferred term, duration of treatment prior to event, rechallenge information, and outcomes.

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

The same approach to safety evaluation will be used for both Part 1 and Part 2.

8.6 Biomarker Analyses

[redacted]

8.7 Subgroup Analyses

Subgroup analyses will be performed for the primary endpoint and selected secondary endpoints by region, virus, age/immunocompromising condition status, age category, and the presence of comorbidities.

Further subgroups may be defined in the SAP.

8.8 Interim Analysis

An unblinded interim analysis will be conducted by an independent statistical team and provided to the IDMC to make a non-binding recommendation based on the criteria described in the table below. The interim analysis will be conducted after 250 participants have been enrolled and have completed the 28-day follow-up period.

Criterion	Recommendation
The RRR for mortality is less than [redacted]	Stop the study for futility
Otherwise	Enrol an additional 300 participants

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The study may also be stopped due to other criteria, such as a low observed event rate, low probability of success or other factors. Full details of the stopping criteria will be outlined in the IDMC charter.

Analyses of some secondary efficacy endpoints may also be provided for to the IDMC for consideration in any recommendation of futility in addition to the criteria above.

8.9 Independent Data Monitoring Committee

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

The IDMC will be responsible for safeguarding the interests of study participants, assessing the safety of the interventions during the study, reviewing the efficacy data at the time of the interim analysis of Part 2, and for making recommendations about the conduct of the study. This will include providing recommendations about necessary changes to the study protocol and/or whether to stop or continue the study.

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

The IDMC will review selected safety data and will advise on the conduct of the study:

- At the end of Part 1, Cohort 1, which may include dosing of additional participants in Cohort 1, initiation of the optional Cohort 2, initiation of Part 2 or study termination.

  And

- At the end of the optional Part 1, Cohort 2, which may include dosing of additional participants in Cohort 2, initiation of Part 2, or study termination.

The IDMC will perform a review of the safety data from Part 2 of the study once 30 participants and again, once 100 participants have completed study treatment. The IDMC will also meet as and when necessary, i.e., if a safety issue arises or when the IDMC or the Sponsor request a further meeting. At the time of the interim analysis, the IDMC will review selected efficacy data and provide recommendation for whether to stop the study for futility or whether to continue enrolment to 550 participants.

The IDMC will be guided by the IDMC Charter. The Charter will define the primary responsibilities of the IDMC, its membership, and the purpose and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and proper communication and outline the contents of the reports that will be provided to the IDMC.

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8.10 Safety Review Committee

The SRC will consist, at a minimum, of Synairgen's Chief Medical Officer, the Chief Investigator, and the PI or delegate.

Following the sentinel dosing for both Part 1, Cohort 1, and for the optional Part 1, Cohort 2, the SRC will review the safety data and, if there is no apparent safety concern, approve the dosing for the remaining participants.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Quality Control (Monitoring)

In order to verify that the study is conducted in accordance with the study protocol, ICH GCP, local regulatory requirements, and other applicable guidelines, data will be monitored at regular intervals. This will allow the Sponsor to ensure that the data is authentic, accurate, and complete. Source data will be verified either on site or remotely. The study Monitoring Plan provides further details on specific monitoring activities.

9.2 Quality Assurance

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

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

10 DATA HANDLING AND RECORD KEEPING

10.1 Source Documents and Electronic Case Report Form

It is possible that source data may be captured in different locations, for example, participant medical records or directly onto other source documents. The PI is responsible for ensuring the accuracy of the data entered into the eCRF from the source documents.

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

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10.2 Record Retention

Essential documents as defined by ICH GCP are not limited to, but include, all signed protocols and any amendment(s), copies of the completed source documents, signed ICFs/other records of informed consent from all participants who consented, hospital records, emergency 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 and study correspondence.

Unless other local law requires archiving for a longer period, the Sponsor and the Investigator shall archive the content of the clinical study master file for at least 25 years after the end of the clinical study. However, the medical files of participants shall be archived in accordance with national law.

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

11 REGULATORY AND ETHICS

11.1 Regulatory and Ethics Considerations

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

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

11.2 Competent Authority Approval

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

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

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

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

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has been received, the Sponsor (or delegate) will release the study medication and participant recruitment can commence.

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

11.4 Informed Consent and Screening Data

Participant ICFs will be provided by the Sponsor and will be approved by the IRB/IEC. Any changes requested by the IRB/IEC must be approved by the Sponsor (or delegate) prior to the documents being used.

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

11.5 Participant Confidentiality

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

The Investigator(s) and the Sponsor or its authorised representative will preserve the confidentiality of all study participants, in accordance with current GCP, federal, state, and local regulations, including, to the extent applicable, the Health Insurance Portability and Accountability Act of 1996.

The Investigator (or delegate) should keep a confidential log of the names of all participants and the participant numbers that they have been allocated to enable identification of the participant, should this be required for safety purposes. Documents not for submission to the Sponsor (e.g., signed ICFs) should be maintained by the Investigator in strict confidence.

11.6 Investigator Compliance

The Investigator and delegated members of the study team must be familiar with the study protocol, the IB, the conduct of the study, and be suitably trained and qualified to conduct their delegated tasks and their responsibilities 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 participants, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/IEC and regulatory authority (where required) notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human participant.

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,

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contact will be made before the implementation of any changes. Any deviations from the protocol will be fully documented in the CROs Clinical Trial Management System (ClinTrak).

11.7 Progress Reports and Safety Reports

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

12 DEFINITION OF END OF STUDY

End of Study is defined as: Last Participant, Last Visit or Long-term Follow-up (Day 42 [28 days post final dose]).

13 SPONSOR DISCONTINUATION CRITERIA

13.1 Study Sites

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

13.2 Entire Study

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

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

14 PUBLICATION OF STUDY RESULTS

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

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

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

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

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

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

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15 APPENDICES

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Appendix A: APACHE II score

Physiologic Variable		+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature - rectal (°C)		≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure (mm Hg)		≥160	130-159	110-129		70-109		50-69		≤49
Heart Rate		≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory Rate (nonventilated or ventilated)		≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation (mmHg) a. $FiO_2 > 0,5$ use A-aDO_2 b. $FiO_2 < 0,5$ use PaO_2	a	≥500	350-499	200-349		<200				
	b					> 70	61-70		55-60	<55
Arterial pH		≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum Sodium (mmol/l)		≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum Potassium (mmol/l)		≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum Creatinine (mg/dl, Double point score for acute renal failure)		≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)		≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White Blood Count (in 1000/mm³)		≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow-Coma-Scale (GCS)		Score = 15 minus actual GCS								
Serum HCO_3 (venous, mmol/l, use if no ABGs)		≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
A = Total Acute Physiology Score APS		Sum of the 12 individual variable points								
B = Age Points		C = Chronic Health Points								
≤44 years 0 points 45-54 years 2 points 55-64 years 3 points 65-74 years 5 points ≥75 years 6 points		If the patient has a history of severe organ system insufficiency or is immunocompromised assign points as follows: a. For nonoperative or emergency postoperative patients – 5 points b. For elective postoperative patients – 2 points								
APACHE II Score = Sum of A (APS points) + B (Age points) + C (Chronic Health points)										

From Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29 [21]

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Appendix B: mSOFA Score

The modified, five-component Sequential Organ Failure Assessment score (excluding the neurological sub-score) is used to determine the level of organ dysfunction while the participant is in the intensive care unit.

Respiratory system

PaO_2/FiO_2 [mmHg (kPa)]	SOFA score
≥400 (53.3)	0
<400 (53.3)	+1
<300 (40)	+2
<200 (26.7) **and** mechanically ventilated	+3
<100 (13.3) **and** mechanically ventilated	+4

FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of oxygen in arterial blood; SOFA: sequential organ failure assessment

Cardiovascular system

Mean Arterial Pressure or Administration of Vasopressors Required	SOFA score
MAP ≥70 mmHg	0
MAP <70 mmHg	+1
dopamine ≤5 µg/kg/min or dobutamine (any dose)	+2
dopamine >5 µg/kg/min OR epinephrine ≤0.1 µg/kg/min OR norepinephrine ≤0.1 µg/kg/min	+3
dopamine >15 µg/kg/min OR epinephrine >0.1 µg/kg/min OR norepinephrine >0.1 µg/kg/min	+4

MAP: mean arterial pressure; SOFA: sequential organ failure assessment

Liver

Bilirubin (mg/dl) [µmol/L]	SOFA score
<1.2 [<20]	0
1.2–1.9 [20-32]	+1
2.0–5.9 [33-101]	+2
6.0–11.9 [102-204]	+3
>12 [>204]	+4

Coagulation

Platelets×10^3/µl	SOFA score
≥150	0
<150	+1
<100	+2
<50	+3
<20	+4

SOFA: sequential organ failure assessment

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Kidneys

Creatinine (mg/dl) [µmol/L] (or urine output)	SOFA score
<1.2 [<110]	0
1.2–1.9 [110-170]	+1
2.0–3.4 [171-299]	+2
3.5–4.9 [300-440] (or <500 ml/d)	+3
>5.0 [>440] (or <200 ml/d)	+4

SOFA: sequential organ failure assessment

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