Safety and efficacy of inhaled SNG001 (IFN-β1a for nebulisation) for the treatment of patients with confirmed SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, pilot trial

Phillip D Monk PhD, Richard J Marsden BA, Victoria J Tear PhD, Jody Brookes BSc, Toby N Batten MSc, Marcin Mankowski MD, Felicity J Gabbay FMedSci, Donna E Davies PhD, Stephen T Holgate FMedSci, Ling-Pei Ho PhD, Tristan Clark MD, Ratko Djukanovic MD, Tom MA Wilkinson PhD, on behalf of the Study Group*

Synairgen Research Ltd., Southampton General Hospital, Southampton, UK (Dr PD Monk, PhD, Dr RJ Marsden, BA; Mrs J Brookes, BSc; Dr VJ Tear, PhD; Professor ST Holgate, FMedSci), NIHR Southampton Biomedical Research Centre, University Hospital Southampton and Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Sir Henry Wellcome Laboratories Southampton, UK (Professor DE Davies, PhD; Professor ST Holgate, FMedSci; Dr T Clark, MD; Professor R Djukanovic, FRCP; Professor TMA Wilkinson, PhD), MRC Human Immunology Unit, MRC Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Headington, UK (Professor L-P Ho, PhD), TranScrip Partners, Wokingham, UK (Dr M Mankowski, MD; Dr Felicity J Gabbay, FMedSci), Veramed Limited, Regal House, Twickenham, UK (Mr TN Batten, MSc).

Corresponding Author:

Professor Tom MA Wilkinson

NIHR Southampton Biomedical Research Centre

University Hospital Southampton

Clinical and Experimental Sciences, Faculty of Medicine

University of Southampton, Sir Henry Wellcome Laboratories

Southampton UK

Email: T.wilkinson@soton.ac.uk

Tel: 02381 205341

*See separate file

Summary

Background SARS-CoV-2 infection carries significant risk of severe and prolonged illness; treatment options are limited. We assessed the efficacy and safety of inhaled SNG001 (nebulised interferon beta-1a) as a therapy for patients hospitalised with COVID-19.

Methods We performed a randomised, double-blind, placebo-controlled, pilot trial at nine UK sites. Adults hospitalised with COVID-19 symptoms, with a positive PCR and/or point-of-care test, were randomly (1:1) assigned to receive SNG001 (6 MIU) or placebo by inhalation via a mouthpiece daily for 14 days. The primary outcome was change in clinical condition using the Ordinal Scale for Clinical Improvement (OSCI) during the dosing period in the intention-to-treat population (ITT). Multiple analyses were performed to identify the primary method for future clinical trials. Secondary outcomes included changes in symptoms by the breathlessness, cough and sputum scale (BCSS). Safety was assessed by collecting adverse events for 28 days. The trial is registered with Clinicaltrialsregister.eu, 2020-001023-14, and ClinicalTrials.gov, NCT04385095; the pilot trial of hospitalised patients is now completed.

Findings The trial was conducted between March 30th and May 30th 2020. 101 patients were randomised; 48 received SNG001 and 50 received placebo (ITT population). Sixty-six (67·3%) patients required oxygen supplementation at baseline. Patients receiving SNG001 had greater odds of improvement across the OSCI scale (OR 2·32; 95% CI: 1·07, 5·04; p=0·033) and were more likely to recover to "no limitation of activity" during treatment (HR 2·19; 95% CI: 1·03, 4·69; p=0·043). SNG001 reduced patient-reported BCSS (difference -0·8, 95% CI: -1·5, -0·1; p=0·026), mainly by lowering the breathlessness score (difference -0·6, 95% CI: -1·0, -0·2; p=0·007). There were three deaths in the placebo and none in the SNG001 group.

The most common serious adverse events were related to COVID-19 and they were respiratory failure (SNG001: three patients [6·3%], placebo: six patients [12·0%]) and pneumonia (SNG001: three patients [6·3%], placebo: three patients [6·0%]).

Interpretation Patients receiving SNG001 had greater odds of improvement and recovered more rapidly, providing a strong rationale for further trials. SNG001 was well-tolerated.

Funding: Synairgen Research Ltd, UK.

Keywords: COVID-19; interferon beta 1a; SARS-COV-2; Ordinal Scale for Clinical Improvement; Breathlessness, Cough and Sputum Scale; treatment; randomised trial

Abstract word count: 326

Manuscript word count: 4,799

Research in context

Evidence before this study

Interferons are cytokines that modulate immune responses to viral infection. The type I interferons (interferon alphas and interferon beta [IFN-β]) have been tested against coronavirus infections *in vitro* with encouraging results. IFN-β-mediated anti-viral responses have been shown to be compromised in people susceptible to COVID-19, such as the elderly or those suffering with chronic airway diseases. Furthermore, SARS-CoV-2 suppresses cellular IFN production, limiting the strength of the initial innate immune response.

Exogenous use of inhaled IFN-β1a (SNG001) in patients with asthma with respiratory viral infections enhances antiviral responses and improves lung function. These properties may facilitate improvement and/or recovery in patients with COVID-19, a severe, viral, respiratory disease where the need for an effective therapeutic intervention is paramount. The aim of the present study was to evaluate the potential effects of an inhaled IFN-β1a formulation in patients hospitalised with confirmed SARS-CoV-2 infection.

Added value of this study

Our study is a randomised, double-blind, placebo-controlled, clinical trial to assess the effect of inhaled IFN-β1a (SNG001) as add-on therapy in adults hospitalised with COVID-19. In the ITT population, SNG001 increased the odds of improvement in clinical status (OSCI), enhanced the likelihood of recovery to 'no limitation of activities' and reduced breathlessness. SNG001 was also well-tolerated when compared with placebo.

Implications of all the available evidence

The present pilot trial serves as a proof-of-concept that inhaled IFN-β1a can attenuate the clinical consequences of COVID-19. The trial was conducted in a small sample; future larger studies in patients with COVID-19 are needed to confirm the potential of SNG001 as an effective treatment.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new virus and the cause of the coronavirus disease (COVID)-19 pandemic, causes a spectrum of clinical presentations, ranging from asymptomatic infection to life-threatening illness. [1] More severe disease is characterised by infection of the lower respiratory tract, pneumonia and respiratory failure, which results in death in about 0.5% of confirmed cases. [2]

In view of the rapid and relentless spread of COVID-19 around the globe, there is a pressing need to develop new treatments. Evidence-based therapy is currently limited to remdesivir, an anti-viral agent which has shown benefits in hospital discharge rate, [3] and dexamethasone, a broad-spectrum anti-inflammatory, offering benefit in patients already requiring respiratory support. [4]

In all virus infections, especially those caused by novel strains where there is little to no established adaptive immunity to the pathogen, the infected host is very dependent on innate immune responses to limit the severity of illness once infection occurs. Essential to this innate response is the action of interferons (IFNs), key orchestrators of the anti-viral immune response with both potent anti-viral and immuno-modulatory functions. [5] The type I interferon, interferon beta (IFN-β), is one of the first cytokines induced by viral infection of a cell and is a primary driver of innate immune responses in the human lung. [6] SARS-CoV-2 directly suppresses the release of IFN-β *in vitro*, [7] and a recent clinical study of patients with COVID-19 demonstrated significantly depressed levels of IFN activity in patients who developed more severe disease. [8] At-risk groups, such as those with comorbidities, the elderly, and recipients of immune suppressive medication, produce less IFN-β, contributing to the risk of more severe lung disease.[9,10]

SNG001 is a formulation of IFN-β for inhaled delivery by nebuliser in development for the treatment of virus-induced lower respiratory tract illnesses. The route of delivery was selected with the aim of achieving sufficiently high concentrations of IFN-β in the lungs that would result in a robust local antiviral response whilst limiting systemic exposure to IFN-β which is associated with flu-like symptoms. [11,12] Inhaled SNG001 is well-tolerated in clinical studies conducted to date involving 230 patients with asthma and/or COPD. [11,13] In those patients, we have shown that SNG001 boosts lung antiviral defences, as assessed by sputum cell antiviral biomarkers both in patients with and without respiratory viral infections. [11,14] In two phase 2 trials, SNG001 had a significantly greater beneficial effect on lung function than placebo in patients with asthma with symptoms of respiratory viral infection. [11,15]

The existing clinical data for inhaled SNG001, coupled with the known suppression of IFN-β by SARS-CoV-2, provided the rationale to conduct a randomised, double-blind, placebo-controlled, phase 2, pilot trial to determine whether inhaled SNG001 has the potential to reduce the severity of lower respiratory tract illness and accelerate recovery in patients with COVID-19. The design of this trial was based on the World Health Organization (WHO) R&D Blueprint Novel Coronavirus COVID-19 Therapeutic Trial Synopsis [16] issued at the time.

Methods

Study design and participants

This was a randomised, double-blind, placebo-controlled, multi-centre, phase 2, pilot clinical trial in patients with confirmed SARS-CoV-2 infection which compared SNG001 and placebo given once daily for up to 14 days, with post-treatment follow-up for a maximum of 28 days.

The trial was conducted at nine UK sites in accordance with the protocol (see online material for the current version of the protocol, including changes from previous versions) 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 Research Governance Framework, the Medicines for Human Use (Clinical Trials) Regulations 2004 and the ethical principles that have their origin in the Declaration of Helsinki. All patients provided either written or verbal informed consent. Safety data were reviewed and monitored by an independent data safety monitoring committee. The trial protocol was reviewed and approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and an Independent Ethical Committee and site Hospital Boards where the trial was conducted (REC Number 20/NW/0168).

Eligible participants were adults aged 18 years or older; admitted to hospital due to COVID-19 symptoms; all with a confirmed SARS-CoV-2 test result in an NHS diagnostic, qualitative reverse transcription polymerase chain reaction (RT-PCR) assay or a positive point-of-care test (FebriDx, Lumos Diagnostics) within the previous 24 hours. [17] Patients were required to understand the information provided in the consenting process and to be willing to give consent. Exclusion criteria were: inability to use a nebuliser with a mouthpiece (including ventilated patients and patients in intensive care); pregnancy or

intention to become pregnant and breastfeeding (for a complete list of inclusion and exclusion criteria, see appendix pp 2–3). During the trial, in version 3 of the protocol, the inclusion criteria were amended to allow inclusion based on "Positive virus test for SARS-CoV-2 using RT-PCR or positive point-of-care viral infection test in the presence of strong clinical suspicion of SARS-CoV-2 infection". This change was made to prevent a delay in patient enrolment while waiting for the PCR results.

Randomisation and masking

After eligibility was confirmed and consent obtained, patients were allocated a unique patient identification number (appendix pp 3) and assigned to one of two treatment groups according to a double-blind, randomisation (1:1) schedule: active intervention (SNG001) or placebo, administered along with local standard of care treatment. Simple randomisation was performed manually using sealed envelopes, with trained clinical research staff assigning the patient the next available randomisation number on the randomisation list. Study investigators, all research and analysis teams and patients were masked to treatment allocation.

SNG001 (containing the active substance, recombinant IFN-β1a) and placebo (with the same formulation as SNG001, excluding the active substance) were identical in appearance. The study medications were presented as ready-to-use aqueous solutions in pre-labelled syringes according to regulatory requirements. Further information on the investigational medicinal product is provided in the appendix (pp 3).

Procedures

Medical history and demographic data were collected prior to dosing. Patients underwent evaluation in the domains of clinical frailty (mobility, energy, physical activity, and function),

vital signs (temperature, respiratory rate, heart rate, systolic blood pressure and oxygen saturations), physical examination (including chest auscultation) with clinical assessment, assessments for pneumonia, the Ordinal Scale for Clinical Improvement [OSCI], see Table 1) and the Breathlessness, Cough And Sputum Scale [BCSS], [18] as well as blood haematology and chemistry. Patients also had a 12-lead electrocardiogram. Chest X-rays were performed if clinically required.

SNG001 (6 MIU IFN-β1a) or placebo were delivered via the I-neb nebuliser (Philips Respironics) once daily for up to 14 days (appendix pp 3). During the 14-day treatment phase and whilst hospitalised, vital signs and levels of consciousness or evidence of confusion and/or agitation were recorded twice daily. In addition, assessment for pneumonia by chest auscultation (and other forms of physical examination if deemed necessary by the investigator), and OSCI and BCSS were conducted daily. OSCI assessments, blood sampling, and 12-lead electrocardiogram assessments (and chest X-rays, if required) were performed 24 hours (±1 day) after the patient's last dose. The use of concomitant medications was recorded throughout the study. Patients were also regularly assessed for signs or symptoms that might be considered adverse events related to the investigational medicinal product. If a patient was discharged from hospital during the study, the assessments were performed by telephone/video link or by email, where feasible. Patients underwent a final outcome assessment 14 days (±3 days) after the patient's last dose.

Outcomes

The primary endpoint, as defined in the protocol, was change in condition using the World Health Organisation (WHO) OSCI (Table 1) during the dosing period in the ITT population.

Secondary endpoints included the change in BCSS score and the investigational drug safety and tolerability.

Statistical analysis

The sample size of 100 patients (50 per arm) used in this pilot stage was based on the WHO recommendations that a pilot phase with 100 patients would be sufficient to inform follow on clinical research. [16] No formal power calculations were performed. Analysis followed a pre-specified statistical analysis plan under an intention-to-treat (ITT; all randomised patients who received at least one dose of study drug); informal hypothesis testing was conducted at the 5% α-level with 95% confidence intervals presented in all analyses. As no prior clinical data had been collected using the OSCI in the study population, the most appropriate way of analysing and interpreting the OSCI was unknown. It was, therefore, considered inappropriate to select a single primary analysis method for this pilot study. Multiple analyses were conducted to explore death, worsening, improvement and recovery from disease, both at fixed time points and over the dosing period, with the aim of identifying the most appropriate statistical method for future clinical trials. There was no hierarchy across analyses or adjustments made for multiplicity.

All analyses described below were adjusted for age, sex, presence of comorbidity, OSCI score at baseline (categorised as ≤3 and ≥4), race (categorised as White and non-White) and duration of prior symptoms (categorised <10 days and ≥10 days). Analyses of OSCI data were conducted over the treatment period or at each individual visit, as appropriate. For OSCI, the treatment period was defined as 16 days, which included the 14-day dosing period and an end of treatment visit on Day 15 or Day 16.

Analysis of improvement across the OSCI scale was performed using an ordered logistic regression model assuming proportional odds.

Severe disease or death (OSCI ≥5), intubation or death (OSCI ≥6) and death (OSCI=8) were analysed using logistic regression models. *Post hoc* analyses of these endpoints using Firth logistic regression were also performed, due to data separation issues observed following study unblinding. Times to first severe disease or death, to first intubation or death and to death were analysed using Cox proportional hazard models. Time to OSCI recovery (defined as OSCI≤1 without rebound) and time to hospital discharge (defined as OSCI≤2 without rebound) were analysed using Fine and Gray's sub-distribution hazard model fitted with death as a competing event. Sustained recovery and sustained hospital discharge were also analysed using logistic regression models.

A last-observation-carried-forward (LOCF) approach was used to impute missing data for analyses of sustained recovery, sustained hospital discharge and improvement.

Breathlessness and cough scores and total BCSS score were analysed using mixed models for repeated measures (MMRM). Data from the follow-up visits or early withdrawal visits after Day 16 were not included in the analysis. Missing breathlessness symptom scores were imputed as 4 ("Severe") for patients receiving mechanical ventilation (OSCI ≥5). Analysis of sputum scores was not planned because COVID-19 is characterised by a dry, non-productive cough.

Safety endpoints were described as frequencies (%).

Due to the exploratory nature of this phase of the study, statistical determinations of p values and confidence intervals were not adjusted for multiple testing. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Trial registration

This trial is registered with Clinicaltrialsregister.eu (number: 2020-001023-14) and ClinicalTrials.gov (number: NCT04385095).

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation and writing of the report. The corresponding author and co-authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 30th and May 30th 2020, 116 patients were screened, of whom 101 were enrolled into the study (CONSORT diagram, Figure 1). Of these, 48 and 50 patients received SNG001 and placebo, respectively, and were included in the ITT population. All but one patient had a positive PCR test for SARS-CoV-2. This patient initially had a positive point-of-care test so was eligible for inclusion into the study, but was negative in a subsequent PCR test. Forty-three patients in each treatment group were included in the per protocol population (all the patients who had SARS-CoV-2 infection confirmed by RT-PCR test, took at least two out of their first three scheduled doses and had no protocol deviations impacting on efficacy). Thirty-nine (81·3%) SNG001 and 36 (72·0%) placebo patients were followed up for the full duration of the study. Results are presented for the ITT population.

Demographic and baseline characteristics, including comorbidities, severity of disease, duration of symptoms, and smoking status are presented in Table 2. Patients' mean (SD) age was 57·1 (13·26) years; 58 (59·2%) were male and 78 (79·6%) were Caucasian. Just over half of the patients (53 [54·1%]) had baseline comorbidities of hypertension, cardiovascular disease, diabetes, chronic lung condition or cancer. In general, patients in the treatment groups were well-matched by baseline characteristics, apart from disease severity measured using the OSCI and the frequencies of specific comorbidities. Patients in the SNG001 group had more severe disease as judged by 37 (77·1%) patients receiving oxygen therapy (OSCI ≥4) compared to 29 (58·0%) patients in the placebo group (Table 2). More patients in the placebo group compared to the SNG001 group had diabetes (9 [33·3%] vs 3 [11·5%]) or cardiovascular disease (8 [29·6%] vs 5 [19·2%]), respectively, and fewer had hypertension (11 [40·7%] vs 18 [69·2%]), respectively.

The median duration of COVID-19 symptoms prior to initiation of treatment was 10·0 days (IQR: 7·0–11·0).

Patients' OSCI score may have changed from time of randomisation to the time of baseline assessment which may have occurred later in the day. At baseline, two (2·0%) patients were receiving non-invasive ventilation or high flow oxygen (OSCI=5), 64 (65·3%) were receiving oxygen by mask or nasal prongs (OSCI=4), 30 (30·6%) were not receiving oxygen therapy (OSCI=3), and two patients were hospitalised for reasons of isolation or quarantine and not because of the severity of their disease; one (1·0%) patient had a baseline OSCI score of 2 ("limitation of activities"), and one (1·0%) patient had a baseline OSCI score of 1 ("no limitation of activities").

The analysis results for the primary endpoint of OSCI change over the dosing period are described below and summarised in Table 3. Results for the follow-up visit on Day 28 are also presented.

The odds of improvement across the entire OSCI scale were more than two-fold greater in the SNG001 group than the placebo group on Day 16 (OR 2·32; 95% CI: 1·07, 5·04; p=0·033; Figure 2) and more than three-fold greater on Day 28 (OR 3·15; 95% CI: 1·39, 7·14; p=0·006; Figure 2).

Three patients died during the study; all deaths occurred in patients randomised to placebo, therefore, no modelling analysis was performed. Eleven (22·4%) patients in the placebo group developed severe disease or died (OSCI ≥5) between the first dose and Day 16 compared with six (12·8%) patients in the SNG001 group. SNG001 reduced the odds of developing severe disease or dying by 79·0% (OR 0·21; 95% CI: 0·04, 0·97; p=0·046), using the pre-specified logistic regression analysis. As quasi-complete separation of data was

observed in some model covariates, an additional*, post hoc*, Firth logistic regression analysis was performed in which the difference between groups was not statistically significant (72·0% reduction; OR 0·28; 95% CI: 0·07, 1·08; p=0·064; Table 3).

In the placebo group, five (10·0%) patients either underwent intubation or died (OSCI ≥6) between the first dose and Day 16 versus three (6·3%) in the SNG001 group. There was no statistically significant difference between treatment groups on the odds of intubation or the time to intubation or death (Table 3).

Over the 14-day treatment period, patients in the SNG001 group were more than twice as likely to recover compared with those in the placebo group (HR 2·19; 95% CI: 1·03, 4·69; p=0·043; Figure 3). On Day 28 (final outcome assessment visit), 28 (58·3%) patients in the SNG001 group and 17 (34·7%) in the placebo group had recovered (Figure 3). The odds of recovery on Day 28 were over three-fold greater in the SNG001 group compared with the placebo group (OR 3·58; 95% CI: 1·41, 9·04; p=0·007; Figure 2).

On Day 16, 33 (68.8%) patients in the placebo group and 35 (72.9%) patients in the SNG001 group had been discharged from hospital. By Day 28, 39 (81·3%) patients had been discharged in the SNG001 group compared with 36 (75·0%) in the placebo group. There was no statistically significant difference between treatment groups in the odds of hospital discharge or the time to hospital discharge (Figures 2 and 4).

Patients in the SNG001 group showed a greater improvement in the secondary endpoint analysis of total BCSS score compared to placebo (SNG001 – placebo difference=-0·8; 95% CI: -1·5, -0·1; p=0·026; Figure 5). Improvement in patient-reported breathlessness on the 0 (no symptoms) to 4 (severe symptoms) score, was greater in the SNG001 group, compared to the placebo group over the treatment period (difference=-0·6; 95% CI:-1·0, -0·2; p=0·007;

Figure 5). Improvement in patient-reported cough over the same period was better, but not statistically significant for SNG001 patients (difference=-0·2; 95% CI: -0·5, 0·1; p=0·285; Figure 5). Scores indicated that sputum production was not a problematic symptom for patients in this study (Figure 5).

Results for the per protocol population were generally stronger (Table 3) with statistically significant effects for SNG001 treatment compared to placebo for improvement across the OSCI on Day 16 (OR 2·80; 95% CI 1·21, 6·52; p=0·017), odds of severe disease or death (OSCI ≥5) on Day 16 (OR 0·18; 95% CI: 0·04, 0·93; p=0·041; *post hoc* Firth logistic regression analysis), time to recovery over the treatment period (HR 2·29; 95% CI 1·07, 4·91; p=0·033), odds of recovery by Day 16 (OR 3·18; 95% CI: 1·21, 8·39; p=0·019) and a trend towards earlier hospital discharge over the treatment period (HR 1·53; 95% CI: 0·96, 2·42; p=0·072).

Twenty-six (54·2%) and 30 (60·0%) patients experienced treatment-emergent adverse events (TEAEs) in the SNG001 and the placebo groups, respectively (Table 4). The most frequently reported TEAE was headache, which was reported in seven patients (14·6%) in the SNG001 group and five patients (10·0%) in the placebo group (see appendix pp 4, Table E1). Fewer patients experienced serious adverse events (SAEs) in the SNG001 group than the placebo group (SNG001: seven [14·6%] patients, placebo: fourteen [28·0%] patients). The most common SAEs were related to COVID-19: respiratory failure (SNG001: three [6·3%] patients, placebo: six [12·0%] patients) and pneumonia (three [6·3%] patients in the SNG001 and three in the placebo group [6·0%]). TEAEs related to treatment were more common in the SNG001 group than the placebo group (SNG001: seven [14·6%] patients, placebo: two [4·0%] patients); cough, reported by two patients (4·2%), was the most frequently occurring treatment-related TEAE in the SNG001 group. Other TEAEs

related to SNG001, each occurring in one patient, included: decreased oxygen saturation, diarrhoea, dry throat, oral pain, night sweats and tremor. Three TEAEs led to study withdrawal in three patients in the placebo group: nausea, multiple organ dysfunction syndrome (fatal) and pulmonary embolism (fatal); none was considered treatment-related. In addition to the fatal TEAEs above, a third patient in the placebo group died with cause of death recorded as COVID-19 pneumonia (considered unrelated to study treatment).

Discussion

This study is a randomised, placebo-controlled trial evaluating the safety and efficacy of inhaled SNG001, an IFN-β1a nebuliser solution, in patients hospitalised with COVID-19. The results of this multicentre, phase 2, pilot trial have shown that SNG001, given as a daily inhaled dose of 6 MIU via nebuliser for 14 days, was associated with greater odds of improvement across the WHO OSCI and more rapid recovery to a point where patients were no longer limited in their activity, with a greater proportion of patients recovering during the 28-day study period. There was a trend towards reduced odds of progression to severe disease or death in the ITT population that became significant in the per protocol population. Secondary endpoint analysis of symptoms revealed a greater improvement in breathlessness and total BCSS over the treatment period on the active treatment.

In keeping with previous observations in patients with asthma [11] and COPD, [19] nebulised SNG001 was well-tolerated. More patients experienced SAEs in the placebo group when compared to the SNG001 group. The most common SAEs in both treatment groups were related to COVID-19. The most common TEAE in the SNG001 group was headache. TEAEs considered related to treatment were infrequent, with cough being the only treatment-related TEAE in the SNG001 group that occurred in more than one (two) patients. Three patients died in the placebo group; there were no deaths in patients receiving SNG001.

The findings in this trial suggest the potential utility of SNG001 in treating COVID-19 in hospitalised patients, which should be explored in a Phase 3 trial. Currently, treatment options for COVID-19 remain limited with the only evidence-based therapies being limited to remdesivir and dexamethasone. [3,4] Despite the use of these therapies, clinical outcomes remain poor. Dexamethasone is only indicated in patients who already require respiratory support (oxygen with or without mechanical ventilation), with a numerically poorer

outcome seen in patients with less severe disease. [4] Remdesivir reduced time to discharge by median 4 days and improved the ordinal scale score at 15-day assessment in one trial, [3] but in two subsequent large studies this clinical benefit was not apparent. [20,21] There is clearly a need for additional therapeutic options for patients with COVID-19 and the results here suggest that inhaled IFN-β may be such a treatment, if our results are confirmed in future trials.

Injectable drug products containing IFN-α and IFN-β have been used in clinic for many years. In the context of highly pathogenic coronavirus strains including SARS-CoV-2, IFN-β has been shown to be more potent than IFN-α. [22,23] Two forms of recombinant IFN-β are available. SNG001 contains IFN-β1a, which is produced in mammalian cells, shares the same amino acid sequence as naturally occurring IFN-β, and has a higher specific activity than IFN- β1b, which is produced in non-mammalian cells. [24] SNG001 is inhaled via a mesh nebuliser which maintains drug activity post aerosolisation. [11] The rationale for this route of administration is to enable maximal delivery of the active drug to the biological focus of SARS-CoV-2 infection, the respiratory epithelium. [25] Recent pragmatic studies [26] and ongoing randomised-controlled trials are seeking to explore the effects of injected type I IFNs in COVID-19. The REMAP-Cap, focusing on patients in the intensive care setting, [27] and the SOLIDARITY and DisCoVeRy trials [28,29] in hospitalised patients are at present trialling injected IFN-β1a and have yet to show whether and to what extent systemic delivery is effective and well-tolerated. Given the greater bioavailability of inhaled drugs at the lung epithelium, such concentrations could be matched only by giving extremely high doses of injected drug with the risk of unacceptable intolerability, suggesting the inhaled route is likely to provide better antiviral outcomes. Such an approach was taken in a recent analysis of an uncontrolled exploratory study of nebulised IFN-α2b, reported in a hospital setting in Wuhan, China,

indicating a positive effect on viral load and the inflammatory biomarkers, interleukin-6 and C-reactive protein, albeit an imbalance in age between treated patients and controls. [30,31] More recently, a similar, pragmatic, open study reported clinical benefits with aerosol inhalation of IFN-κ plus trefoil factor 2, with reductions in viral shedding, and duration of symptoms and hospital stay. [32] Taken together with our study, these results suggest potential antiviral benefit of aerosolised IFN therapy in COVID-19. The value of this approach may be driven, in part, by the evasive nature of SARS-CoV-2 on natural type I IFN production which is more profound than with other comparable respiratory pathogens. [8,33] The optimal route and specific type of IFN may depend on the stage of disease, the spread of viral infection beyond the lung, and the ease of administration in different clinical settings.

The timing of IFN treatment for COVID-19 has been the subject of considerable debate, with concerns being raised that later IFN treatment may cause or exacerbate the cytokine storm observed in the later stages of severe disease. For example, to avoid concerns over potential pro-inflammatory effects of IFN, in an open-label study of injected IFN-β1b in a triple combination with lopinavir-ritonavir and ribavirin for the treatment of COVID-19, investigators limited treatment with IFN to within 7 days of symptom duration onset. [26] It was concluded that triple antiviral therapy was safe and superior to lopinavir-ritonavir combination in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19. In our study, patients had a median duration of symptoms of 10 days at recruitment and SNG001 was given daily to patients for 14 days. Importantly, we found that SNG001 was well-tolerated and showed clinical benefit, suggesting that there is a substantially greater window for effective treatment.

Further trials in different clinical settings, including in ventilated patients or in pre-hospital care, are warranted or underway. [34] With the threat of a second wave of COVID-19 coinciding with the winter incidence of cold and influenza in the Northern Hemisphere, development of broad spectrum anti-viral agents, such as IFN-β, which boost local lung defences rather than target specific viral mechanisms, may carry significant additional benefits to patients and to overburdened healthcare systems alike and this will also require studying. [5,22]

Our clinical trial has a number of limitations. As a pilot study of a novel medicine in a hospitalised patient group its sample size is limited, making the generalisability of the findings to wider populations and healthcare systems, where standard of care may vary, challenging. The OSCI at the time of the study was a new tool and its performance in randomised controlled trials of COVID-19 was uncertain. In this pilot study, we elected to assess this outcome in multiple statistical analyses and report them without hierarchy. This enabled exploration of this new tool with the aim of identifying the most appropriate statistical method for future clinical trials. However, this approach introduces the issue of repeat analyses of this outcome which requires consideration in the interpretation of this pilot study result and the need for larger scale, formal testing of a selected approach at the next phase of development. The nebuliser used in this study is not suitable for use in patients requiring ventilation; further studies of SNG001 using alternative delivery devices to include these critically ill patients are warranted. In any small study, not all factors can be evenly balanced during randomisation. In this study, SNG001 and placebo groups were well matched for age, sex, and overall comorbidities, but were less well matched for disease severity at recruitment and for specific comorbid conditions particularly diabetes, cardiovascular disease and hypertension. However, these factors were considered in the

statistical model used and beneficial signals for therapy were enhanced when *a priori* adjustments were made. Phase 3 trials will address these issues through randomisation of larger and more heterogeneous groups. Due to an urgency to deliver a trial result in the setting of the pandemic, the patient follow-up was completed at 28 days, a time point where, interestingly, some of the greatest treatment effects of SNG001 on recovery were observed. Recent evidence suggests that the long-term sequelae of severe COVID-19 are significant, [35] so it will be important to track treatment effects on the prevention and resolution of these symptoms in future trials. Additional sampling beyond core safety parameters was limited by the clinical context of the acute pandemic burden of care. Additional readouts on exploratory inflammatory and virological endpoints may have provided useful information on mechanism of therapeutic response but were not feasible in this setting. Future studies in different clinical settings will enable these analyses to be made.

Five and six patients withdrew consent in the placebo and SNG001 groups, respectively. Whilst there was, therefore, no indication that the treatment was associated with differential withdrawal as similar patient numbers withdrew in both groups, it is important to understand for future studies that significant withdrawal rates may occur in the setting of acute COVID-19 perhaps due to associated complexities of care and uncertainties in outcome.

In conclusion, SNG001, a treatment already studied and proven to be safe in patients with asthma and COPD, has now been shown to be well-tolerated in COVID-19 patients, with a range of clinical outcomes displaying a beneficial pattern of response to SNG001 therapy. These encouraging data provide a strong rationale to urgently conduct larger international

studies in the context of the ongoing clinical burden of COVID-19. In addition to a phase 3 trial of SNG001 in hospitalised patients with COVID-19 who require no more than supplementary oxygen, it may be appropriate to assess the safety and efficacy of SNG001 in ventilated, critically ill COVID-19 patients with evidence of active viral infection in the lungs. In view of the broad anti-viral effects of IFN-β, this trial suggests that the efficacy of SNG001 should also be assessed in the hospital setting against other seasonal respiratory viruses which cause much morbidity and mortality every year, including cases of co-infection with SARS-CoV-2 which threaten to overwhelm healthcare systems during the intensity of seasonal virus seasons.

Contributors

PDM, RJM, VJT, JB, TNB, MM, FJG, DED, STH, TC, RD, and TMAW had substantial contributions to the conception and design of the work. PDM, VJT, JB, TNB, MM, TC, L-PH, and TMAW contributed to the acquisition of the study data. Analysis of the data was performed by PDM, RJM, VJT, JB, TNB, MM, FJG, RD, and TMAW. TNB was responsible for the statistical analysis. FJG was the Chair of the data safety monitoring committee during the study. PDM, RJM, VJT, JB, TNB, MM, FJG, DED, L-PH, STH, TC, RD and TMAW contributed to the interpretation of the data, drafting and revising of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. All authors have read and approved the manuscript.

Declaration of interests

PDM is a Director of Synairgen Research Ltd, is an employee and Director of Synairgen plc (the parent company of Synairgen Research Ltd), and own shares and holds share options in Synairgen plc; in addition PDM has a patent GB 2011216.5 pending. RJM is a Director of Synairgen Research Ltd, is an employee and Director of Synairgen plc and own shares and holds share options in Synairgen plc. VJT is an employee of Synairgen Research Ltd and holds share options in Synairgen plc; in addition, VJT has a patent GB 2011216.5 pending. JB is an employee of Synairgen Research Ltd and holds share options in Synairgen plc. MM reports fees as a consultant from Synairgen Research Ltd, outside the submitted work. FJG is a Managing Partner of Transcrip Partners and reports personal fees from TranScrip Partners who supported Synairgen for the study and personal fees from TranScrip Partners outside of this work; FGJ was also a member of the independent data safety monitoring committee.

DED reports that she is a co-founder of Synairgen Research Ltd, owns shares in Synairgen plc, and has received personal fees and other fees as a consultant to Synairgen Research Ltd during and outside of the conduct of the trial; in addition, DED has a grant from Boehringer Ingelheim for unrelated to the trial fibrosis studies and has patents Anti-virus therapy for respiratory diseases (PCT/GB2005/050031) and Interferon-beta for anti-virus therapy for respiratory diseases (WO2005087253A3) with royalties paid to the University of Southampton and the inventors. STH reports that he is co-founder of Synairgen Research Ltd, owns shares, and has received personal fees as a Non-executive Director and Consultant of Synairgen Research Ltd outside the submitted work; in addition, STH has patents: Interferon-beta for anti-virus therapy for respiratory diseases, (WO2005087253A3 WIPO [PCT] issued), Anti-virus therapy for respiratory diseases (US20090257980A1 issued), and Inhaled IFN beta for COVID-19 (pending); he is also Chair of the Academy of Medical Sciences for the report "Preparing for a challenging winter 2020/21"; 14 July 2020. L-PH reports receiving funds from Synairgen Research Ltd to carry out phase 1 clinical trial at her institution during the conduct of the study and grants from Celgene for research study in fibrosis, outside the submitted work. TC reports receipt of personal fees from BioMerieux and BioFire LLC, Roche, Janssen, Cidara Therapeutics, Synairgen Research Ltd and Randox diagnostics; non-financial support from BioMerieux and BioFire LLC and Qiagen; and other fees from Synairgen Research Ltd outside the submitted work. RD reports receiving fees for lectures at symposia organised by Novartis, AstraZeneca and TEVA, consultation fees for TEVA and Novartis as member of advisory boards and participation in a scientific discussion about asthma organised by GlaxoSmithKline; RD is a co-founder, current consultant and owns shares in Synairgen Research Ltd, a University of Southampton spin out company. TMAW reports receipt of personal fees and other from MMH, grants and personal fees from

GlaxoSmithKline; grants and personal fees from AstraZeneca; personal fees from BI; grants and personal fees from Synairgen Research Ltd outside the submitted work. TNB has nothing to declare.

Data sharing

The data analysed and presented in this study are available from the corresponding author on reasonable request, providing the request meets local ethical and research governance criteria after publication. Patient-level data will be anonymised and study documents will be redacted to protect the privacy of trial participants. The trial protocol is provided in the supplemental appendix (pp 5).

Acknowledgements

This study was supported from Synairgen Research Ltd, UK. TMAW is supported in part by the NIHR Southampton BRC. L-PH is supported in part, by the NIHR Oxford BRC. We would like to thank all the patients who volunteered for the study and clinical and research teams at all the participating clinical centres and the NIHR Respiratory Translational Research Collaboration (RTRC) for support in trial delivery. We are grateful to Dr Antigoni Ekonomou of Niche Science & Technology Ltd for medical writing services and editorial assistance with the manuscript. We thank also Dr Alastair Watson for helping with the manuscript preparation and coordination of the submission.

References

1. Guan W-j, Ni Z-y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**(18): 1708–1720.
2. Salje H, Tran Kiem C, Lefrancq N, et al. Estimating the burden of SARS-CoV-2 in France. *Science* 2020; **369**: 208–211.
3. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; **395**: 1569–1578**.**
4. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* 2020; published online July 17. DOI: 10.1056/NEJMoa2021436.
5. Li S, Gong M, Zhao F, et al. Type I Interferons: Distinct Biological Activities and Current Applications for Viral Infection. *Cell Physiol Biochem* 2018; **51**: 2377–2396.
6. Watson A, Spalluto CM, McCrae C, et al. Dynamics of IFN-β responses during respiratory viral infection: insights for therapeutic strategies. *Am J Respir Crit Care Med* 2020; **201**: 83–94.
7. Yuen C-K, Lam J-Y, Wong W-M, et al. SARS-CoV-2 nsp13, nsp14, nsp15 and orf6 function as potent interferon antagonists. *Emerg Microbes Infect* 2020; **9**: 1418–1428.
8. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* 2020; **369**: 718–724.
9. Agrawal A. Mechanisms and implications of age-associated impaired innate interferon secretion by dendritic cells: a mini-review. *Gerontology* 2013; **59**: 421–426.
10. Singanayagam A, Loo S-L, Calderazzo M, et al. Antiviral immunity is impaired in COPD patients with frequent exacerbations. *Am J Physiol Lung Cell Mol Physiol* 2019; **31**7: L893–L903.
11. Djukanović R, Harrison T, Johnston SL, et al. The effect of inhaled IFN-β on worsening of asthma symptoms caused by viral infections. A randomized trial. *Am J Respir Crit Care Med* 2014; **190**: 145–154.
12. Filipi ML, Beavin J, Brillante RT, et al. Nurses' perspective on approaches to limit flu-like symptoms during interferon therapy for multiple sclerosis. *Int MS Care* 2014; **16**: 55–60.

13. Clinical Trials.gov. A study to test a potential new treatment for COPD patients suffering from the common cold or influenza. https://clinicaltrials.gov/ct2/show/NCT03570359 [Accessed August 17, 2020].
14. Reynolds S, Lunn K, Beegan R, Tear V, Monk PD. Antiviral biomarkers are upregulated in sputum cells following administration of inhaled interferon beta to COPD patients. *Eur Respir J* 2019; **54** (suppl 63): OA263. DOI: 10.1183/13993003.congress-2019.OA263 (abstr).
15. McCrae C, Olsson M, Aurell M, et al. On-demand inhaled interferon-beta 1a for the prevention of severe asthma exacerbations: results of the INEXAS phase 2a study. In D12. Immunotherapy In Lung Disease: *Am J Respir Critical Care Med* 2018; **201**: A6165 (abstr).
16. World health Organisation (WHO) R&D Blueprint and Coronavirus. COVID-19 Therapeutic Trial Synopsis. 2020. https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis [Accessed August 25, 2020].
17. National Health System (NHS). Guidance and standard operating procedure. COVID-19 virus testing in NHS laboratories Publications approval reference: 001559, 16th March 2020. https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/guidance-and-sop-covid-19-virus-testing-in-nhs-laboratories-v1.pdf [Accessed August 20, 2020].
18. Leidy NK, Rennard SI, Schmier J, Jones MK, Goldman M. The breathlessness, cough, and sputum scale: the development of empirically based guidelines for interpretation. *Chest* 2003; **124**: 2182**–**2191.
19. Synairgen plc press release: Synairgen announces positive data from interim analysis of SNG001 trial in COPD patients. September 2020. https://www.synairgen.com/wp-content/uploads/2020/09/200908-SG015-Press-Release-Final.pdf [Accessed September 23, 2020].
20. Goldman JD, Lye DCB, Hui DS, et al; GS-US-540-5773 Investigators. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med* 2020; published online May 27. DOI:10.1056/NEJMoa2015301.
21. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA* 2020; published online August 21. DOI:10.1001/jama.2020.16349.

22. Mantlo E, Bukreyeva N, Maruyama J, Paessler S, Huang C. Antiviral activities of type I interferons to SARS-CoV-2 infection. *Antiviral Res* 2020; **179**: 104811; published online April 29. DOI: 10.1016/j.antiviral.2020.104811.
23. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Treatment of SARS with human interferons. *Lancet* 2003; **362**: 293–29410.
24. Runkel L, Meier W, Pepinsky RB, et al. Structural and Functional Differences Between Glycosylated and Non-glycosylated Forms of Human Interferon-β (IFN-β). *Pharm Res* 1998; **15**: 641–649.
25. Schaefer IM, Padera RF, Solomon IH, Kanjilal S, Hammer MM, Hornick JL, Sholl LM. In situ detection of SARS-CoV-2 in lungs and airways of patients with COVID-19. *Mod Pathol* 2020; published online June 19. DOI: 10.1038/s41379-020-0595-z.
26. Hung IF, Lung KC, Tso EY, et al Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* 2020; **395**: 1695–1704.
27. Clinical Trials.gov. Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP). April 13, 2016. https://www.clinicaltrials.gov/ct2/show/NCT02735707 (Accessed August 18, 2020).
28. World health Organisation (WHO) "Solidarity" clinical trial for COVID-19 treatments. July 6 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments (Accessed August 18, 2020).
29. Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. Type 1 interferons as a potential treatment against COVID-19. *Antiviral Res* 2020; **178**: 104791.
30. Zhou Q, Chen V, Shannon CP, et al. Interferon-α2b Treatment for COVID-19. *Front Immunol* 2020; **11**: 1061. Published online May 15. DOI: 10.3389/fimmu.2020.01061.
31. Hao SR, Yan R, Zhang SY, et al. Interferon-α2b spray inhalation did not shorten virus shedding time of SARS-CoV-2 in hospitalized patients: a preliminary matched case-control study. *J Zhejiang Univ Sci B* 2020; **21**: 628–636.

32. Fu W, Liu Y, Xia L, et al. A clinical pilot study on the safety and efficacy of aerosol inhalation treatment of IFN-κ plus TFF2 in patients with moderate COVID-19. *EClinicalMedicine* 2020; published online July 29. DOI: 10.1016/j.eclinm.2020.100478.
33. Blanco-Melo D, Nilsson-Payant BE, Liu W-C, et al. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. *Cell* 2020; **181**: 1036–1045.e1039.
34. Clinical Research in Southampton. People with early COVID-19 symptoms sought for at home treatment trial. July 17 2020. https://www.uhs.nhs.uk/ClinicalResearchinSouthampton/Research/News-and-updates/Articles/People-with-early-COVID-19-symptoms-sought-for-at-home-treatment-trial.aspx (Accessed August 19, 2020).
35. Rovere Querini P, De Lorenzo R, Conte C, et al. Post-COVID-19 follow-up clinic: depicting chronicity of a new disease. *Acta Biomed* 2020; **91**: 22–28.

Table 1 World Health Organization Ordinal Scale for Clinical Improvement

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

ECMO = extracorporeal membrane oxygenation; RRT= renal replacement therapy

Table 2 Demographic and Baseline Characteristics

	Placebo (N=50)	SNG001 (N=48)	Total (N=98)
Age at inclusion, years, mean (SD)	56·5 (11·94)	57·8 (14·60)	57·1 (13·26)
Sex, n			
Male	31 (62·0%)	27 (56·3%)	58 (59·2%)
Female	19 (38·0%)	21 (43·8%)	40 (40·8%)
Ethnicity, n			
Caucasian	39 (78·0%)	39 (81·3%)	78 (79·6%)
Non-Caucasian	11 (22·0%)	9 (18·7%)	20 (20·4%)
Comorbidities, n	27 (54·0%)	26 (54·2%)	53 (54·1%)
Hypertension	11 (40·7%)	18 (69·2%)	29 (54·7%)
Chronic lung condition	12 (44·4%)	11 (42·3%)	23 (43·4%)
Cardiovascular disease	8 (29·6%)	5 (19·2%)	13 (24·5%)
Diabetes	9 (33·3%)	3 (11·5%)	12 (22·6%)
Cancer	1 (3·7%)	0	1 (1·9%)
Severity of disease at baseline,* n			
No limitations of activities	1 (2·0%)	0	1 (1·0%)
Limitation of activities	1 (2·0%)	0	1 (1·0%)
Hospitalised (no oxygen therapy)	19 (38·0%)	11 (22·9%)	30 (30·6%)
Oxygen by mask, or nasal prongs	28 (56·0%)	36 (75·0%)	64 (65·3%)
Non-invasive ventilation, or high flow oxygen	1 (2·0%)	1 (2·1%)	2 (2·0%)
Duration of symptoms, days**	9.5 (7·0–12·0)	10.0 (8·0–11·0)	10.0 (7·0–11·0)
Current smoking status, n			
Currently uses tobacco	1 (2·0%)	1 (2·1%)	2 (2·0%)
Former smoker	16 (32·0%)	11 (22·9%)	27 (27·6%)
Never smoked	33 (66·0%)	36 (75·0%)	69 (70·4%)

Data are presented for the intent-to-treat population. SD = standard deviation

*Severity of disease at baseline followed Ordinal Scale for Clinical Improvement (OSCI).

** Duration of symptoms is presented as median (min, max).

Table 3 Analysis of Ordinal Scale of Clinical Improvement During the Dosing Period

Analysis	ITT population		PP Population	
	Ratio (95% CI)	p-value	Ratio (95% CI)	p-value
Odds of improvement across the OSCI	OR 2·32 (1·07, 5·04)	0·033	OR 2·80 (1·21, 6·52)	0·017
Time to severe disease or death (OSCI ≥5)	HR 0·50 (0·18, 1·38)	0·179	Not calculated	
Odds of severe disease or death (OSCI ≥5)	OR 0·28 (0·07, 1·08)	0·064*	OR 0·18 (0·04, 0·93)	0·041*
Time to intubation or death (OSCI ≥6)	HR 0·38 (0·09, 1·65)	0·198	Not calculated	
Odds of intubation or death (OSCI ≥6)	OR 0·42 (0·09, 1·83)	0·246*	OR 0·31 (0·05, 1·79)	0·189*
Time to Recovery	HR 2·19 (1·03, 4·69)	0·043	HR 2·29 (1·07, 4·91)	0·033
Odds of Recovery	OR 3·19 (1·24, 8·24)	0·017	OR 3·18 (1·21, 8·39)	0·019
Time to Hospital Discharge	HR 1·37 (0·85, 2·20)	0·196	HR 1·53 (0·96, 2·42)	0·072
Odds of Hospital Discharge	OR 1·63 (0·61, 4·35)	0·330	OR 2·14 (0·64, 7·12)	0·215

Odds ratios relate to the end-of-treatment visit on Day 15 or 16. Time to event analyses include all data up to and including the end-of-treatment visit. Recovery was defined as a post baseline OSCI score of 0 or 1 which does not rise above 1 at any subsequent visits. Hospital discharge was defined as a post baseline OSCI score of 2 or less which does not rise above 2 at any subsequent visits. Three patients died during the study; all deaths occurred in patients randomised to placebo, therefore, no modelling analysis was performed. ITT = intention-to-treat. PP = per protocol. OR = odds ratio. HR = hazard ratio.

* *Post hoc* analysis using Firth logistic regression analysis.

Table 4 Summary of Treatment Emergent Adverse Events

	Placebo (N=50)	SNG001 (N=48)
Any TEAE, n	30 (60.0%)	26 (54·2%)
Any TEAE during treatment period	25 (50·0%)	23 (47·9%)
Any serious TEAE	14 (28·0%)	7 (14·6%)
Any treatment–related TEAE	2 (4·0%)	7 (14·6%)
Any fatal TEAE	3 (6·0%)	0
Any TEAE that led to study withdrawal	3 (6·0%)	0

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

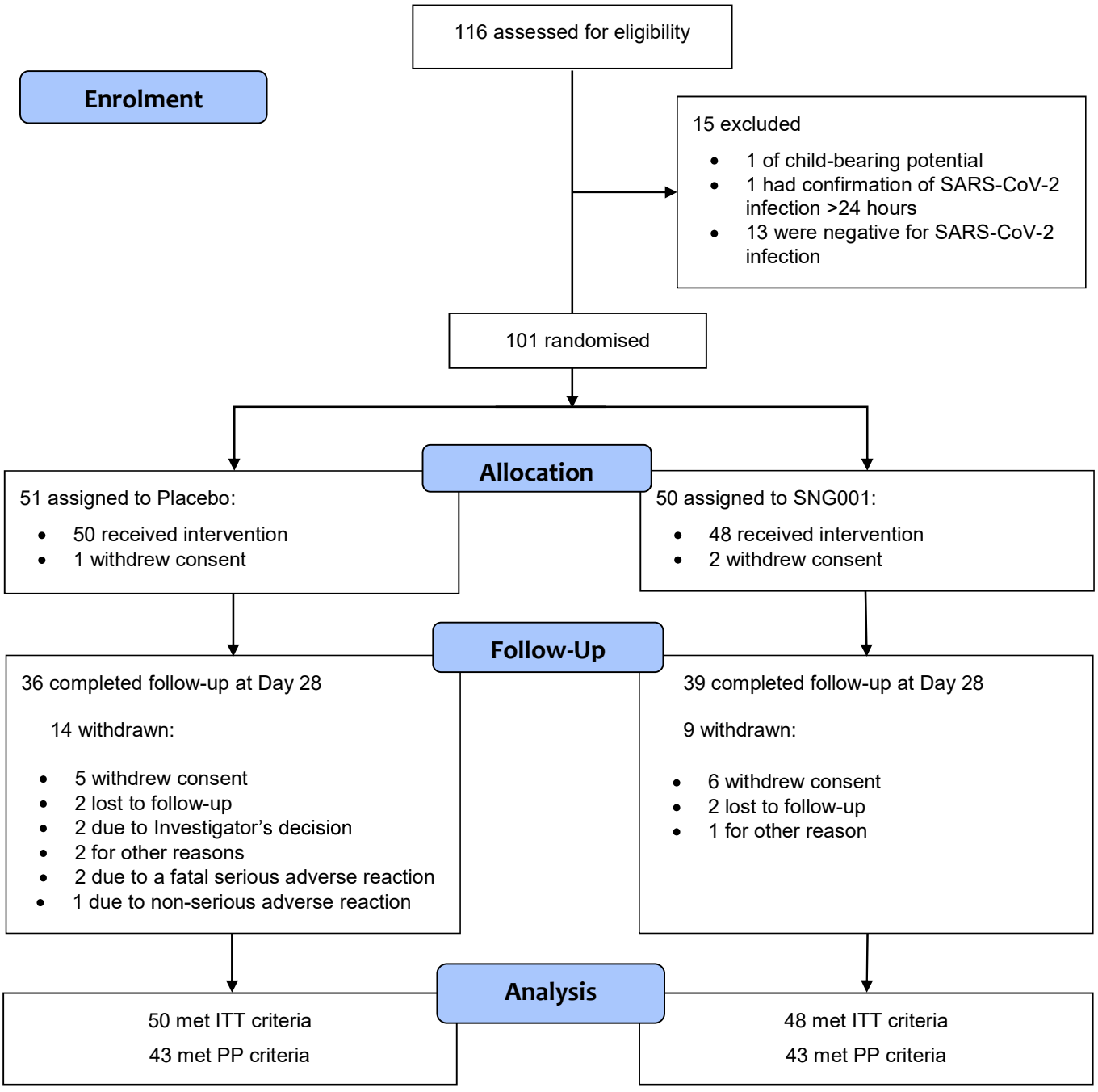

Figure 1 CONSORT Flow Diagram

Eligible patients were randomised 1:1 to intervention (SNG001) or placebo. ITT = intent-to-treat; PP = per protocol.

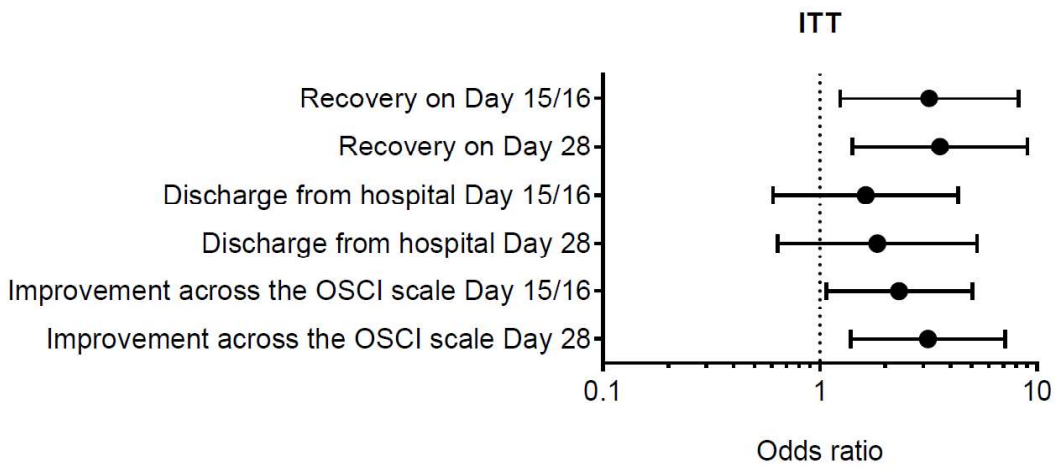

Figure 2 Odds Ratios of Recovery (OSCI ≤1), Hospital Discharge and Improvement

Odds ratios of recovery (defined as unchanged post baseline OSCI score of 0 or 1; OR 3·19, 95% CI: 1·24, 8·24, p = 0·017), hospital discharge (OR 1·63, 95% CI: 0·61, 4·35, p = 0·330) and improvement (OR 2·32; 95% CI: 1·07, 5·04; p = 0·033) on the World Health Organization Ordinal Scale of Clinical Improvement on Days 15 or 16 (end-of-treatment visit) are indicated. Odds of recovery (OR 3·58; 95% CI: 1·41, 9·04; p = 0·007), hospital discharge (OR 1·84; 95% CI: 0·64, 5·29; p = 0·257) and improvement (OR 3·15; 95% CI: 1·39, 7·14; p = 0·006) on Day 28 (follow-up visit), are also shown. Comparisons were made between the SNG001 (n = 48 patients) and placebo (n = 50 patients) groups in the intention-to-treat (ITT) population.

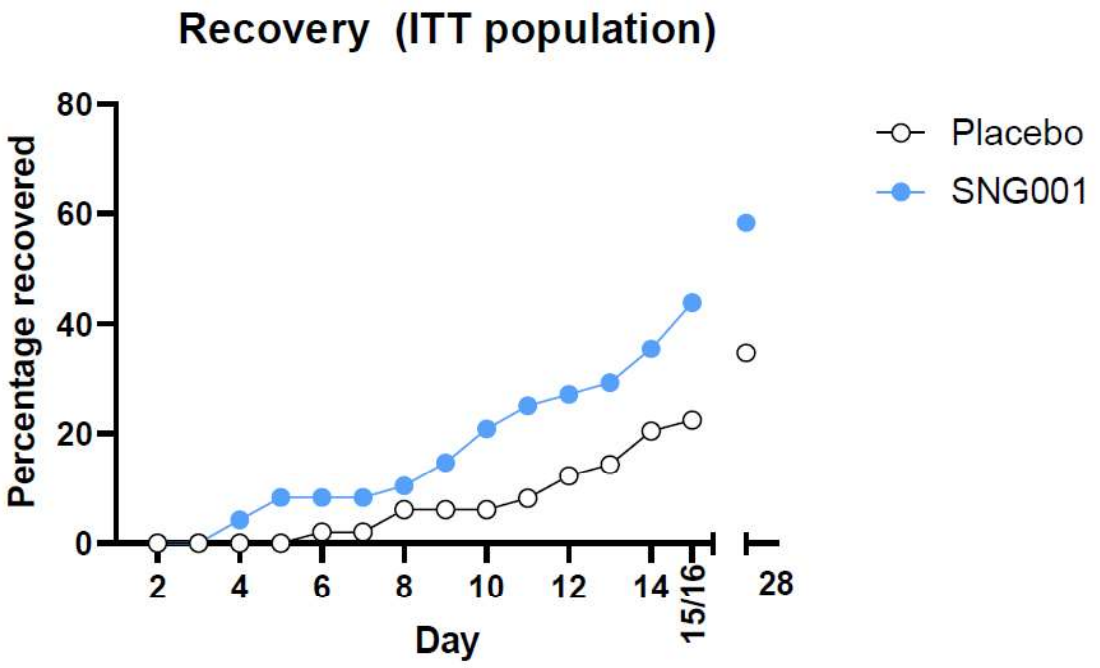

Figure 3 Patient Recovery (OSCI ≤1) During the Study

Percentage of patients who recovered (defined as having an unchanged post baseline OSCI score of 0 or 1) up to Day 15 or 16 (end-of-treatment visit) and on Day 28 (follow-up visit) is presented for the intention-to-treat (ITT) population (SNG001: n = 48; placebo: n = 50).

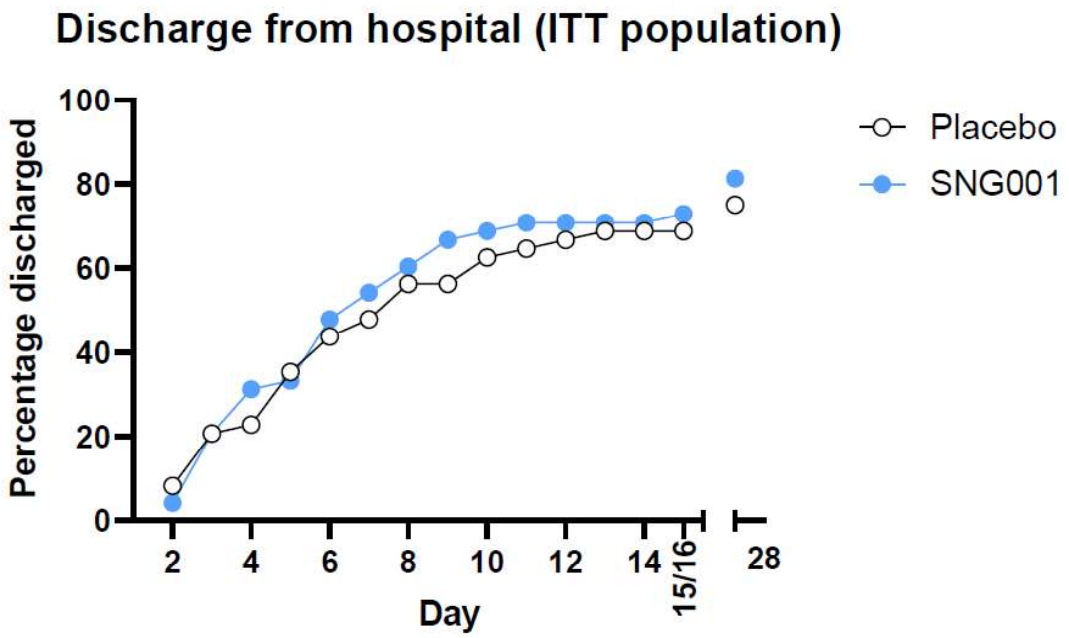

Figure 4 Hospital Discharge

Percentage of patients who were discharged up to Day 15 or 16 (end of treatment visit) and on Day 28 (follow-up visit) is presented for the intention-to-treat (ITT) population (SNG001: n = 48; placebo: n = 50).

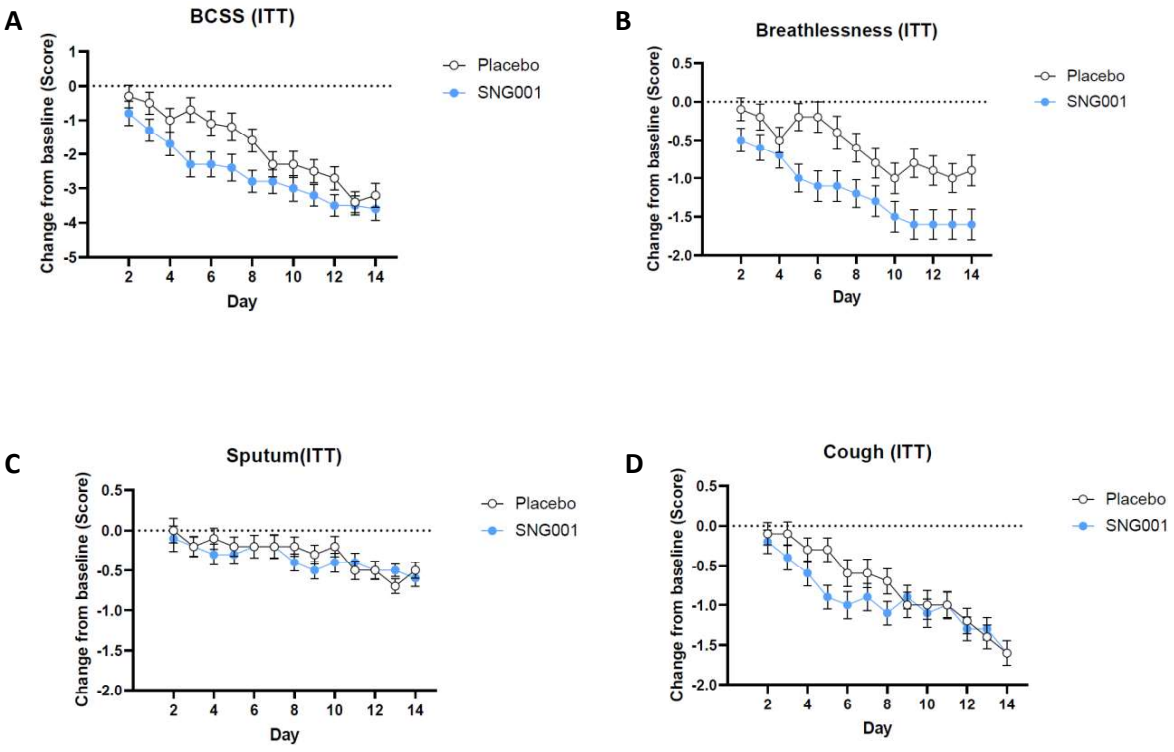

Figure 5 Breathlessness, Cough and Sputum Scale Evaluation

Least squares mean (95% confidence intervals) change from the baseline score up to Day 14 is presented for total breathlessness, cough and sputum Scale (BCSS) scores (A) and individual scores for breathlessness (B), cough (C) and sputum (D) for the intention-to-treat (ITT) population (SNG001: n = 48; placebo: n = 50).