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Early View

Original research article

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Nebulised interferon beta-1a (SNG001) in hospitalised COVID-19: SPRINTER Phase III Study

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Abstract

Background

Despite the availability of vaccines and therapies, patients are being hospitalised with COVID-19. Interferon-β is a naturally-occurring protein that stimulates host immune responses against most viruses, including SARS-CoV-2. SNG001 is a recombinant interferon-β1a formulation delivered to the lungs via nebuliser. SPRINTER assessed the efficacy and safety of SNG001 in adults hospitalised due to COVID-19 who required oxygen via nasal prongs or mask.

Methods

Patients were randomised double-blind to SNG001 (N=309) or placebo (N=314) once-daily for 14 days plus standard of care (SoC). The primary objective was to evaluate recovery after administration of SNG001 versus placebo, in terms of times to hospital discharge and recovery to no limitation of activity. Key secondary endpoints were: progression to severe disease or death; progression to intubation or death; and death.

Results

Median time to hospital discharge was 7.0 and 8.0 days with SNG001 and placebo, respectively (hazard ratio 1.06 [95%CI 0.89, 1.27]; p=0.51); time to recovery was 25.0 days in both groups (1.02 [0.81, 1.28]; p=0.89). There were no significant SNG001–placebo differences for the key secondary endpoints, with a 25.7% relative risk reduction in progression to severe disease or death (10.7% and 14.4%, respectively; odds ratio 0.71 [0.44, 1.15]; p=0.161). Serious adverse events were reported by 12.6% and 18.2% patients with SNG001 and placebo, respectively.

Conclusions

Although the primary objective of the study was not met, SNG001 had a favourable safety profile, and the key secondary endpoints analysis suggested that SNG001 may have prevented progression to severe disease.

Study registration number: ISRCTN85436698

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has highlighted the impact of respiratory viruses on mortality and morbidity and their resulting pressures on healthcare provision. Despite the availability of vaccines and therapies, patients continue to be hospitalised with, and die from, coronavirus disease 2019 (COVID-19) [1, 2], emphasizing the need for treatments with novel mechanisms of action, especially for hospitalised patients.

Interferon-β is a naturally occurring protein that stimulates immune responses critical for the development of host protection against most viruses, including SARS-CoV-2 [3–6]. It is produced as an immediate local response to viral infection, and results in antiviral protein production that limits viral replication [7–9]. SARS-CoV-2 suppresses interferon-β release [10, 11], allowing viral spread throughout the respiratory tract. Furthermore, patients with deficient interferon responses, e.g., due to genetics, aging, comorbidities, or autoantibodies against type I interferons (typically interferon-α and -ω, with a minority of patients having antibodies against interferon-β), are at greater risk of severe viral lung disease [12–15]. Importantly, patients hospitalised due to COVID-19 can have prolonged viral shedding (>17 days), especially those with more severe disease [16]. Overall, therefore, evidence points to the potential for enhancing the host's innate immune response by administering interferon-β into the lungs as an effective treatment against COVID-19 [9].

Injectable and subcutaneous formulations of interferon-β have not demonstrated clinically meaningful effects in COVID-19 [17], possibly because they result in low interferon-β concentrations within the lungs. SNG001 is a unique formulation of recombinant interferon-β1a that contains few excipients and has near-neutral pH, making it suitable for inhaled administration. The aim of delivery via nebuliser is to achieve a high local concentration within the lower respiratory tract, the site of SARS-CoV-2 infection [18]. Inhaled SNG001 has been shown to upregulate antiviral biomarker levels in the lungs of patients with chronic

obstructive pulmonary disease (COPD) or asthma [19–21], and to have potent *in-vitro* antiviral activity against SARS-CoV-2, including a number of variants of concern [22].

In addition to the scientific evidence suggesting the need to restore robust interferon responses, a Phase II study conducted early in the course of the pandemic in patients hospitalised with COVID-19 showed that those who received SNG001 were more likely to improve, and recovered more rapidly, than those who received placebo [23]. This provided the rationale for the current Phase III study (SPRINTER; **S**ARS-CoV-2: **P**hase III T**R**ial of **I**nhaled I**NTER**feron-β Therapy) the aim of which was to evaluate the efficacy and safety of SNG001 in patients hospitalised due to COVID-19 who required oxygen therapy via nasal prongs or a mask, but who did not need high flow oxygen or ventilatory support.

Material and methods

Study design

In this double-blind, placebo-controlled, international study, patients were randomly assigned to SNG001 or matching placebo once-daily via vibrating mesh nebuliser (Aerogen® Solo nebuliser, Dangan, Galway, Ireland) for 14 days. The effect of study treatment was assessed on top of current local standard of care (SoC), with no limitation on concomitant medications for the treatment of COVID-19 or vaccination. Patients discharged during the 14-day treatment phase completed treatment at home, with study staff providing support via telephone or video call. Patients were followed for up to 90 days.

The study was approved by the independent ethics committees or research boards at each institution, performed in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization notes for guidance on Good Clinical Practice (ICH/CPMP/135/95), and registered in the ISRCTN registry (ISRCTN85436698). The protocol was amended four times (supplementary table S1).

Patients

The study recruited males or females, ≥18 years of age, hospitalised due to COVID-19 and requiring oxygen via nasal prongs or mask. Key exclusion criteria were: ongoing SARS-CoV-2 infection that had lasted ≥3 weeks, previous SARS-CoV-2 infection, non-invasive ventilation, high-flow nasal oxygen therapy, endotracheal intubation, and invasive mechanical ventilation (for full list of criteria see supplement). Patients provided informed consent prior to any study-related procedure.

Study procedures

Patients were assigned to treatment according to a randomisation schedule, with investigators and patients blinded to treatment by matching placebo. Study medication was presented in two pre-filled syringes, each containing 0.65 mL of solution (for SNG001 this contained 12 MIU/mL of interferon-β1a). SNG001 dose selection was based on prior clinical

and animal data ([23] and data on file). In the previous Phase II study [23], SNG001 was delivered using the I-neb nebuliser (Philips Respironics, Tangmere, UK), with the administered dose delivering a lung dose of 3.8 MIU; when delivered via the vibrating mesh nebuliser, the same administered dose is predicted to provide a lung dose of approximately 5 MIU (data on file). During nebulisation, supplemental oxygen could be administered via nasal cannula; if this was insufficient, additional oxygen could be administered through the nebuliser's oxygen port.

Prior to administration of the first dose, and daily up to Day 28, the following assessments were completed: World Health Organization (WHO) Ordinal Scale of Clinical Improvement (OSCI) [24]; Breathlessness, Cough and Sputum Scale (BCSS) [25]; National Early Warning Score 2 (NEWS2, only while hospitalised) [26]; and EuroQol 5-dimension 5-level (EQ-5D-5L; on Days 7, 15 and 28 only). COVID-19 symptoms were assessed from Days 1–35, with WHO OSCI and EQ-5D-5L also completed daily from Days 29 to 35. See supplement for details. Adverse events were recorded up to 28 days after the patient's last dose, with physical examinations and vital signs assessed daily while the patient was in hospital.

Outcomes

The primary objective was to evaluate recovery after administration of SNG001 compared to placebo. The two primary endpoints were time to hospital discharge (WHO OSCI score ≤2; sustained for ≥7 days and without readmission prior to Day 35) and time to recovery to no limitation of activity (WHO OSCI score ≤1, sustained for ≥7 days). The study was to be considered successful if SNG001 was statistically superior to placebo for at least one of the primary endpoints. The three key secondary endpoints were: progression to severe disease or death (WHO OSCI score ≥5); progression to intubation or death (WHO OSCI score ≥6); and death, all assessed up to 35 days after first dose.

Other secondary endpoints were: the proportion of patients recovering (WHO OSCI score ≤1 sustained for ≥7 days), discharged from hospital, and with an improvement in WHO OSCI,

each at Days 7, 14, 21, and 28; changes in BCSS total score and individual domains during the treatment period; changes in NEWS2 during the hospitalisation period; daily assessment of COVID-19 symptoms; limitation of usual activities; and quality of life measured using EQ-5D-5L. Safety and tolerability were assessed throughout the study by recording vital signs, adverse events, concomitant medications, and immunogenicity.

Statistical analysis

A sample size of 610 patients (305 per treatment arm) was estimated to provide ≥90% power to detect a hazard ratio (HR) of 1.45 in time to hospital discharge and a HR of 1.70 in time to recovery, with ≥95% power to declare statistical significance on at least one of the primary endpoints. This sample size was calculated using a global two-sided alpha level of 0.05, adjusted with the Hochberg procedure to allow for multiple comparisons. The sample size calculation assumed 70% hospital discharge in the placebo arm at Day 28, 30% recovery in the placebo arm at Day 28, and a dropout rate of 25% over the 28-day evaluation period, with time to dropout exponentially distributed.

The HRs for the two primary endpoints were estimated from Cox proportional hazards models with covariates for age, sex, prior duration of COVID-19 symptoms, geographic region, and COVID-19 vaccination status, with multiplicity controlled by the Hochberg procedure. For the key secondary endpoints, odds ratios (ORs) were estimated using logistic regression models with the same covariates as the primary analyses. See supplement for the other secondary endpoints.

The intention-to-treat (ITT) population, used for the efficacy analyses, comprised all randomised patients. The per-protocol (PP) population, used for supportive analyses of the primary and key secondary endpoints, comprised all patients in the ITT population who did not have any protocol deviations with an impact on efficacy (see results and supplementary table S2). The safety population consisted of the ITT population that received at least one dose of study medication.

Results

The study was conducted between 12 January 2021 and 10 February 2022 at 111 sites in 17 countries. Of 653 patients screened, 623 were randomised, 309 to receive SNG001 plus SoC and 314 to placebo plus SoC, with 234 and 240 patients, respectively, completing treatment (Figure 1). The main reason for exclusion from the PP population was failure to receive at least two doses of study medication in the first three days of treatment (supplementary table S2). Baseline demographics and disease characteristics were similar in the two groups (Table 1).

Outcomes

The median time to hospital discharge in the ITT population was 7.0 (95% CI 7.0, 8.0) days with SNG001 plus SoC, compared to 8.0 (7.0, 9.0) days with placebo plus SoC, with a non-significant HR of 1.06 (0.89, 1.27; p=0.51). Results were similar in the PP population (HR 1.02 [0.84, 1.23]; p=0.85). The median time to recovery to no limitation of activity in the ITT population was 25.0 (22.0, upper CI not calculable) days in both treatment groups, with a non-significant HR (1.02 [0.81, 1.28]; p=0.89). Again, PP population results were similar (HR 1.01 [0.79, 1.29]; p=0.93).

SNG001 plus SoC vs placebo plus SoC differences for the key secondary endpoints were not statistically significant. The proportion of patients who progressed to severe disease or death by Day 35 was 25.7% lower (OR 0.71 [0.44, 1.15]; p=0.161) in the SNG001 plus SoC group compared to the placebo plus SoC group in the ITT population and 36.0% lower (0.63 [0.35, 1.13]; p=0.119) in the PP population (Table 2). Similarly, the proportions of patients who were intubated or died, or who died within 35 days were lower in the SNG001 plus SoC group compared to the placebo plus SoC group. For the other secondary endpoints, there were no prominent differences between the two treatment groups (supplementary tables S3 and S4; supplementary figures S1–S5).

In order to gain further insight into subgroups that may be responsive to treatment, a *post-hoc* analysis of progression to severe disease or death within 35 days (WHO OSCI score ≥5) was conducted, with patients subgrouped by baseline parameters that are associated with an increased risk of severe COVID-19: increased age (≥65 years), ≥1 comorbidity, and poor respiratory function (oxygen saturation ≤92% and/or respiratory rate ≥21 breaths/min while on supplemental oxygen). This analysis was conducted in the PP population so as to focus on the patients who had received study medication and clinical care according to the protocol stipulations. The ORs were higher in all subgroups compared to the overall PP population, especially in patients with poor respiratory function in whom a significant (69.9%; p=0.046) reduction was observed (Figure 2). Given the *post-hoc* nature of these results, with multiplicity not protected, these data should be considered exploratory.

Safety

Overall, a similar proportion of patients in the two treatment groups experienced adverse events, and the most common events were similar in the two groups (Table 3). The majority were not considered related to treatment, and were mild or moderate in severity. Fewer patients in the SNG001 plus SoC group experienced severe or serious adverse events than in the placebo plus SoC group. Of note, pulmonary embolism adverse events were only seen in the placebo group, with five considered serious. There were no marked differences between the two groups in any of the other safety parameters.

Discussion

The primary objective of the study was not met with respect to hospital discharge or recovery to no limitation of activity. The study was not powered to evaluate the three key secondary endpoints related to disease progression, but, although not reaching statistical significance, trends favouring the addition of SNG001 to SoC were observed for each of these measures, including a 26% relative risk reduction in patients progressing to severe disease or death in the SNG001 plus SoC group compared with placebo plus SoC. Furthermore, consistent with previous clinical studies, including those in patients with asthma or COPD [19–21], SNG001 was well tolerated and had a favourable safety profile.

Efficacy analyses were also performed in the PP population, which excluded patients whose treatment deviated from the protocol in a way that may have impacted evaluations. The most common reason for exclusion was not receiving at least two full doses of study medication in the first three days. The relative risk reduction in the patients who progressed to severe disease or death was 36% in the PP population rather than 26% in the ITT population, although this was not statistically significant. Furthermore, in the *post-hoc* subgroup analyses, conducted in patients with baseline clinical parameters associated with increased severe COVID-19 risk, differences in favour of SNG001 plus SoC were more marked than in the PP or ITT populations, with relative risk reductions in progression to severe disease or death ranging from 44.8% (p=NS) to 69.9% (p=0.046) when patients were grouped by age, presence of comorbidities, and poor respiratory function (i.e., oxygen saturation ≤92% and/or respiratory rate ≥21 breaths/min while on supplemental oxygen). This potential clinically important effect therefore needs to be confirmed in a future study adequately powered to assess this endpoint.

The lack of impact on recovery contrasts with the results from the Phase II study of inhaled interferon-β in patients with COVID-19 [23], conducted at the beginning of the COVID-19 pandemic (March to May 2020) before any treatments that had been evaluated in randomised controlled studies were implemented as SoC. Thus, SPRINTER differed from

the previous study in that 18% of the included patients had been fully vaccinated, and that a large proportion were receiving corticosteroids (87%) and/or antivirals (19%). These improvements in SoC, together with changes in hospital practice, may have masked our ability to show a treatment effect on the primary endpoint. One of the consequences of these changes is that patients were discharged from hospital more quickly in the current trial. While in the Phase II study, the median time to hospital discharge in the subgroup of patients who were receiving oxygen by mask or nasal prongs (i.e., matching the population recruited into SPRINTER) was 9 days in the placebo plus SoC group (data on file), it was 8 days in SPRINTER overall, decreasing further to 6 days in the UK sites (where the Phase II study was conducted [data on file]; Figure S6). Improvements in SoC have also been reported by the RECOVERY Collaborative Group. Initially in the RECOVERY platform study, conducted in 2020, 28-day mortality was 23% in patients who received dexamethasone plus SoC [27], whereas in a later study, conducted in 2021, 28-day mortality in the SoC group (with 95% of patients receiving a corticosteroid such as dexamethasone) was 14% [28]. Similarly, the proportion of patients discharged from hospital within 28 days in these groups increased from 67% to 78% [27, 28].

The favourable safety and tolerability profile of SNG001 observed in the SPRINTER study was consistent with the previous studies in patients with COVID-19, asthma and COPD [19–21, 23]. A similar proportion of patients in the two treatment groups experienced adverse events, most of which were mild or moderate in severity, and not considered either treatment-related or serious. In terms of serious adverse events, pulmonary embolism only occurred in the placebo plus SoC group, an observation that is interesting as incidence of coagulation events are well documented for patients hospitalised with COVID-19.

Given the observation, which would need to be confirmed in further studies, that patients with poor respiratory function may gain greater benefit from SNG001, a potential limitation of the study is that patients requiring non-invasive ventilation, high-flow nasal oxygen therapy, endotracheal intubation or invasive mechanical ventilation could not be dosed. However, the

nebuliser can be used in different configurations that should enable these patients to be dosed in future studies (supported by appropriate dose selection studies, taking into account drug delivery to the lungs). In addition, the timing of initiation of interferon treatment has been the subject of debate, with suggestions that later initiation could be less effective. Patients were excluded from the study only if the prior duration of symptoms was ≥3 weeks (although a recent positive SARS-CoV-2 virus test was required, and most patients had a duration of symptoms of less than 10 days). In the previous Phase II study, in which SNG001 was more effective than placebo, the median duration of symptoms at recruitment was similar to the current study [23]. This suggests there is a wide window for initiation of treatment with SNG001.

In conclusion, although the primary objective of the study was not met, there were signals in the key secondary endpoints which suggest that SNG001, on top of SoC, may have prevented progression to severe disease (although differences were not statistically significant). In addition, SNG001 was well-tolerated with a favourable safety profile, validating the route of administration. When combined with the results of the previous Phase II study, these findings provide a rationale to continue investigating SNG001, not only in hospitalised patients with COVID-19 (in the context of ongoing virus evolution and likely emergence of new variants), but also more widely in patients with severe seasonal viral lung infections, due to the broad-spectrum and variant agnostic antiviral activity of interferon-β.

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Conflicts of interest

In addition to the writing support declared above, the authors have the following conflicts of interest to declare.

PDM is an employee of Synairgen Research plc, the parent company of Synairgen Research Ltd (and such costs are met by Synairgen Research Ltd), the sponsor of this trial, and owns shares and has options on shares in Synairgen plc.

JLB is an employee of Synairgen Research Ltd, the sponsor of this trial, and has options on shares in Synairgen plc.

VJT is an employee of Synairgen Research Ltd, the sponsor of this trial, and owns shares and has and has options on shares in Synairgen plc.

TNB provided statistical support, programming and consultancy to Synairgen Research Ltd via a contract with his employer, Veramed Ltd.

MM Provided consulting services to Synairgen Research Ltd, the sponsor of this trial, with all payments made to tranScrip Ltd.

TA-V has no other conflicts of interest to disclose.

MGC has no other conflicts of interest to disclose.

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MK declares the receipt of funding to her institution from Synairgen Research Ltd, the sponsor of this trial. Outside the scope of the trial she declares funds paid to her institution from the National Institutes of Health, American Lung Association, Sanofi-Regeneron and AstraZeneca, consulting fees from AstraZeneca, Sanofi-Regeneron and Genentech, one patent issued and one pending for which she received no funds directly (she is Chief Medical Officer and Co-founder RaeSedo, Inc), funds for the participation in a Data Safety Monitoring Board for the ALUND Study, funds for a leadership role of the National Heart, Lung and Blood Scientific Advisory Council (NIH), and the future receipt of stock options in RaeSedo, Inc.

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FJG declares the receipt of consulting fees paid to tranScrip Ltd from Synairgen Research plc, the sponsor of this trial, and participation in a Data Safety Monitoring Board for Synairgen. She is also president of the Faculty of Pharmaceutical Medicine of three UK Royal College of Physicians.

STH received payments as non-executive director of, and owns shares in, Synairgen plc, the parent company of the sponsor of this trial.

RD declares the receipt of consulting fees and payment for participation in a Data Safety Monitoring Board or Advisory Board from Synairgen Research Ltd, the sponsor of this trial. RD owns shares in Synairgen plc, the parent company of the sponsor of this trial. Outside the trial, he declares payment or honoraria from Regeneron, GlaxoSmithKline and Kymab

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Tables

Table 1. Patient baseline demographics and disease characteristics (intention-to-treat population).

Parameter	Placebo plus SoC (N=314)	SNG001 plus SoC (N=309)
Age, years	53.7 (14.42)	52.0 (15.19)
<40 years	58 (18.5%)	66 (21.4%)
40–64 years	181 (57.6%)	178 (57.6%)
≥65 years	75 (23.9%)	65 (21.0%)
Sex, male	208 (66.2%)	203 (65.7%)
Race		
White	215 (68.5%)	224 (72.5%)
Asian	48 (15.3%)	42 (13.6%)
Black	6 (1.9%)	7 (2.3%)
Other/unknown	45 (14.3%)	36 (11.7%)
Body-mass index, kg/m^2	30.5 (7.48)	29.6 (6.13)
≥30 kg/m^2	131 (41.7%)	112 (36.2%)
Smoking status		
Current smoker or e-cigarette user	19 (6.1%)	15 (4.9%)
Former smoker	79 (25.2%)	76 (24.6%)
Any comorbidity	158 (50.3%)	156 (50.5%)
Cancer	16 (5.1%)	16 (5.2%)
Cerebrovascular disease	8 (2.5%)	5 (1.6%)
Chronic kidney disease	13 (4.1%)	8 (2.6%)
Chronic lung disease	20 (6.4%)	22 (7.1%)
Chronic liver disease	1 (0.3%)	1 (0.3%)
Diabetes (type I or type II)	52 (16.6%)	59 (19.1%)
Heart condition	117 (37.3%)	117 (37.9%)
Mental health disorder	30 (9.6%)	27 (8.7%)
Duration of symptoms at randomisation, days	9.5 (3.66)	9.6 (3.64)
NEWS2 score	4.3 (1.92); N=305	4.3 (1.93); N=302
BCSS score, total	4.6 (2.38)	4.8 (2.54); N=306
COVID-19 vaccination status		
Not vaccinated	224 (71.3%)	231 (74.8%)
Partially vaccinated	30 (9.6%)	24 (7.8%)
Fully vaccinated	60 (19.1%)	54 (17.5%)
COVID-19–related therapy at baseline		
Remdesivir	64 (20.4%)	54 (17.5%)

Parameter	Placebo plus SoC (N=314)	SNG001 plus SoC (N=309)
Corticosteroids	275 (87.6%)	267 (86.4%)
Dexamethasone	229 (72.9%)	216 (69.9%)

Data are mean (standard deviation) or number of patients (%). SoC, standard of care; NEWS2 = National Early Warning System-2, BCSS = Breathlessness, Cough and Sputum Scale

Table 2. Key secondary endpoints, assessed up to Day 35.

Endpoint		**Intention-to-treat**		**Per protocol**	
		Placebo plus SoC (N=314)	**SNG001 plus SoC (N=309)**	**Placebo plus SoC (N=261)**	**SNG001 plus SoC (N=256)**
Patients who progressed to severe disease or death within 35 days	n (%)	45 (14.4%)	33 (10.7%)	32 (12.3%)	20 (7.8%)
	OR (95% CI); p value	0.71 (0.44, 1.15); 0.161		0.63 (0.35, 1.13); 0.119	
	RRR	25.7% reduction		36.0% reduction	
Patients who progressed to intubation or death within 35 days	n (%)	23 (7.3%)	20 (6.5%)	15 (5.7%)	10 (3.9%)
	OR (95% CI); p value	0.85 (0.45, 1.61); 0.610		0.76 (0.34, 1.72); 0.512	
	RRR	11.6% reduction		32.0% reduction	
Patients who died within 35 days	n (%)	17 (5.4%)	14 (4.5%)	12 (4.6%)	7 (2.7%)
	OR (95% CI); p value	0.79 (0.38, 1.67); 0.544		0.65 (0.26, 1.64); 0.363	
	RRR	16.3% reduction		40.5% reduction	

OR and RRR are SNG001 plus SoC versus placebo plus SoC. SoC, standard of care; OR, odds ratio; CI, confidence interval; RRR, relative risk reduction.

Table 3. Treatment-emergent adverse events, overall and most common preferred terms (≥10% patients in either treatment group for adverse events; ≥5% for adverse events considered related to treatment; ≥1% for adverse events leading to discontinuation, or serious, severe or fatal adverse events).

Parameter	Placebo plus SoC (N=303)	SNG001 plus SoC (N=301)
Any adverse event	251 (82.8%)	251 (83.4%)
Headache	61 (20.1%)	71 (23.6%)
Productive cough	72 (23.8%)	70 (23.3%)
Myalgia	60 (19.8%)	60 (19.9%)
Rhinorrhoea	54 (17.8%)	58 (19.3%)
Oropharyngeal pain	47 (15.5%)	55 (18.3%)
Arthralgia	54 (17.8%)	54 (17.9%)
Wheezing	35 (11.6%)	45 (15.0%)
Fatigue	40 (13.2%)	39 (13.0%)
Cough	28 (9.2%)	39 (13.0%)
Chest pain	52 (17.2%)	37 (12.3%)
Dyspnoea	42 (13.9%)	30 (10.0%)
Any adverse event related to treatment	77 (25.4%)	68 (22.6%)
Headache	16 (5.3%)	17 (5.6%)
Any adverse event leading to discontinuation of study treatment	23 (7.6%)	24 (8.0%)
COVID-19 pneumonia	1 (0.3%)	5 (1.7%)
COVID-19	3 (1.0%)	2 (0.7%)
Respiratory failure	3 (1.0%)	5 (1.7%)
Acute respiratory failure	3 (1.0%)	0
Any severe adverse event	42 (13.9%)	34 (11.3%)
Respiratory failure	9 (3.0%)	7 (2.3%)
COVID-19	5 (1.7%)	7 (2.3%)
COVID-19 pneumonia	5 (1.7%)	7 (2.3%)
Pneumonia	0	3 (1.0%)
Dyspnoea	0	3 (1.0%)
Acute respiratory failure	7 (2.3%)	1 (0.3%)
Any serious adverse event	55 (18.2%)	38 (12.6%)
COVID-19	8 (2.6%)	11 (3.7%)
Respiratory failure	9 (3.0%)	9 (3.0%)
COVID-19 pneumonia	8 (2.6%)	8 (2.7%)
Acute kidney injury	2 (0.7%)	3 (1.0%)
Pneumonia	0	3 (1.0%)
Acute respiratory failure	7 (2.3%)	1 (0.3%)
Pulmonary embolism	5 (1.7%)	0

Parameter	Placebo plus SoC (N=303)	SNG001 plus SoC (N=301)
Any serious adverse event related to treatment	3 (1.0%)	3 (1.0%)
Any fatal adverse event	16 (5.3%)	16 (5.3%)
COVID-19	3 (1.0%)	5 (1.7%)
COVID-19 pneumonia	2 (0.7%)	4 (1.3%)
Any fatal adverse event related to treatment	0	0

SoC, standard of care.

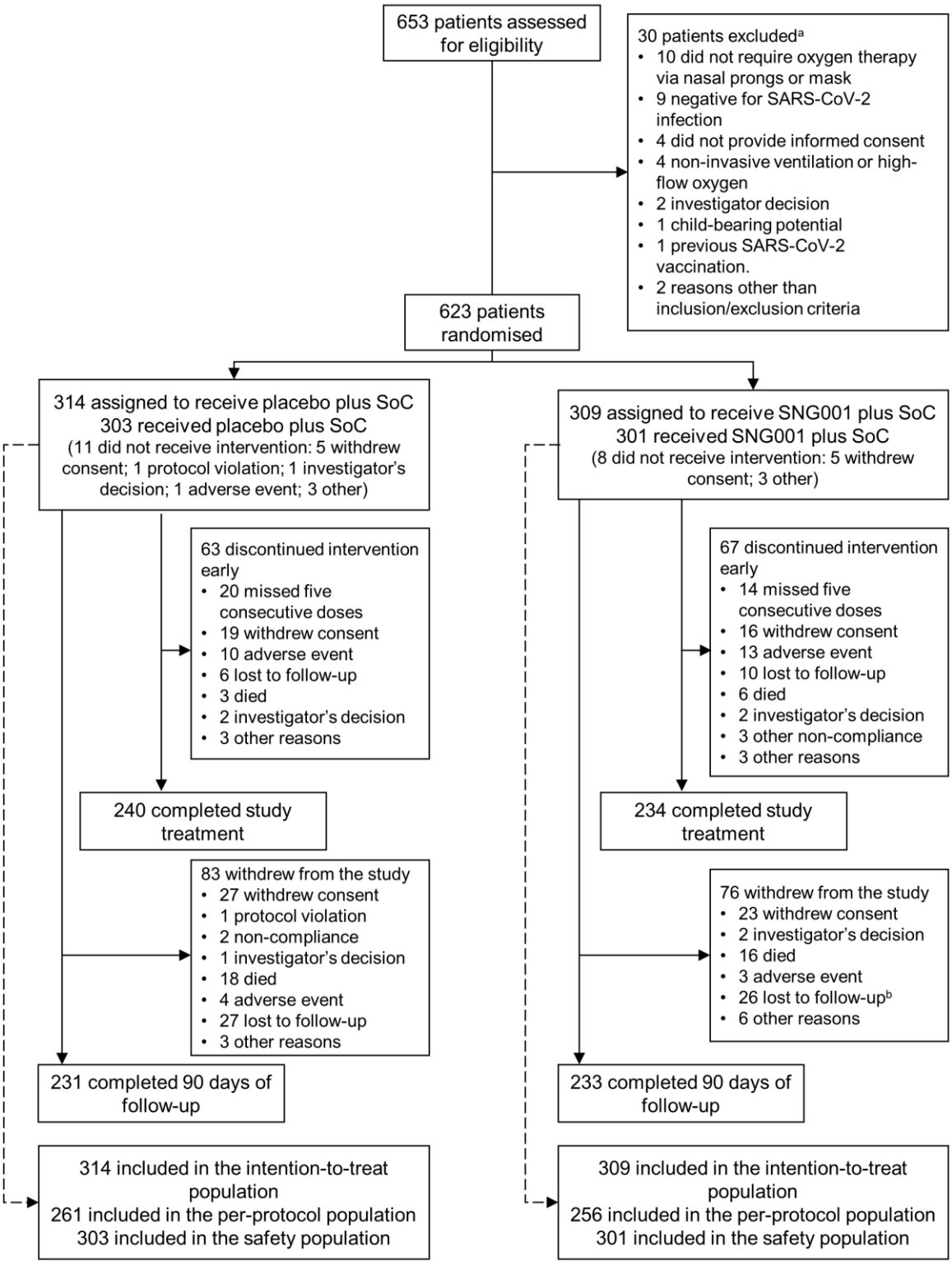
Figure legends

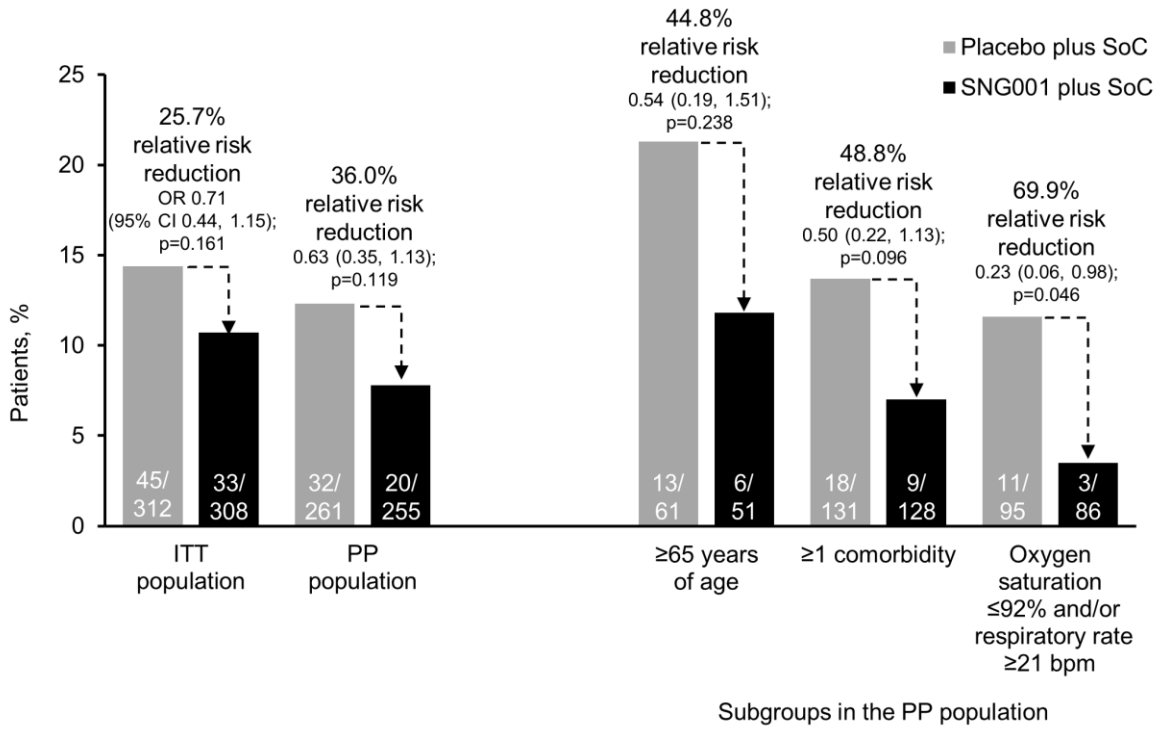
Figure 1. Patient flow through the study.

[a]Patients may be included in more than one category. [b]Two patients in the SNG001 plus SoC group were lost to follow-up during the first 35 days but contact was re-established at Day 90. SoC, standard of care.

Figure 2. Results of post hoc subgroup analyses: Patients who progressed to severe disease or death within 35 days (WHO OSCI score ≥5).

ITT, intention-to-treat; PP, per-protocol; OR, odds ratio; CI, confidence interval; HR, hazard ratio.


653 patients assessed for eligibility
30 patients excluded[a]
• 10 did not require oxygen therapy via nasal prongs or mask
• 9 negative for SARS-CoV-2 infection
• 4 did not provide informed consent
• 4 non-invasive ventilation or high-flow oxygen
• 2 investigator decision
• 1 child-bearing potential
• 1 previous SARS-CoV-2 vaccination.
• 2 reasons other than inclusion/exclusion criteria
623 patients randomised
314 assigned to receive placebo plus SoC
303 received placebo plus SoC
(11 did not receive intervention: 5 withdrew consent; 1 protocol violation; 1 investigator's decision; 1 adverse event; 3 other)
309 assigned to receive SNG001 plus SoC
301 received SNG001 plus SoC
(8 did not receive intervention: 5 withdrew consent; 3 other)
63 discontinued intervention early
• 20 missed five consecutive doses
• 19 withdrew consent
• 10 adverse event
• 6 lost to follow-up
• 3 died
• 2 investigator's decision
• 3 other reasons
67 discontinued intervention early
• 14 missed five consecutive doses
• 16 withdrew consent
• 13 adverse event
• 10 lost to follow-up
• 6 died
• 2 investigator's decision
• 3 other non-compliance
• 3 other reasons
240 completed study treatment
234 completed study treatment
83 withdrew from the study
• 27 withdrew consent
• 1 protocol violation
• 2 non-compliance
• 1 investigator's decision
• 18 died
• 4 adverse event
• 27 lost to follow-up
• 3 other reasons
76 withdrew from the study
• 23 withdrew consent
• 2 investigator's decision
• 16 died
• 3 adverse event
• 26 lost to follow-up[b]
• 6 other reasons
231 completed 90 days of follow-up
233 completed 90 days of follow-up
314 included in the intention-to-treat population
261 included in the per-protocol population
303 included in the safety population
309 included in the intention-to-treat population
256 included in the per-protocol population
301 included in the safety population


Placebo plus SoC
SNG001 plus SoC
Patients, %
25
20
15
10
5
0
25.7% relative risk reduction
OR 0.71 (95% CI 0.44, 1.15); p=0.161
36.0% relative risk reduction
0.63 (0.35, 1.13); p=0.119
44.8% relative risk reduction
0.54 (0.19, 1.51); p=0.238
48.8% relative risk reduction
0.50 (0.22, 1.13); p=0.096
69.9% relative risk reduction
0.23 (0.06, 0.98); p=0.046
45/312
33/308
32/261
20/255
13/61
6/51
18/131
9/128
11/95
3/86
ITT population
PP population
≥65 years of age
≥1 comorbidity
Oxygen saturation ≤92% and/or respiratory rate ≥21 bpm
Subgroups in the PP population

Nebulised interferon beta1a (SNG001) in hospitalised COVID-19: SPRINTER Phase III Study

Phillip D Monk, Jody L Brookes, Victoria J Tear, Toby N Batten, Marcin Mankowski, Tatjana Adzic-Vukicevic, Michael G Crooks, Davinder PS Dosanjh, Monica Kraft, Christopher E Brightling, Felicity J Gabbay, Stephen T Holgate, Ratko Djukanovic, Tom MA Wilkinson, on behalf of the SPRINTER Study Group

Supplement

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Methods

Summary of protocol amendments

Table S1. Summary of protocol amendments.

Amendment number	Amendments	Date
1	Following discussions with regulatory authorities the study design was simplified, with one dose level of SNG001 tested instead of two. Under the previous design, SNG001 was to be administered at the current dose (the contents of two syringes), and at half the current dose (the contents of one syringe), with each SNG001 dose requiring administration of matching placebo. In addition to simplifying dosing, the removal of one dose level also decreased the number of patients required to be recruited. In addition, the order of the key secondary endpoints was altered, an interim analysis was introduced to test for futility, and an antigen test was included as evidence of positive SARS-CoV-2 status. Text was edited for clarity and consistency.	27 Nov 2020
2	Again, following discussions with regulatory agencies, time to hospital discharge was elevated from key secondary to primary endpoint (the study was already sufficiently powered, based on the assumptions for the existing primary endpoint, time to recovery), and the progression to intubation or death, and death secondary endpoints were elevated to key secondary endpoints (with a Hochberg procedure and gatekeeping strategy added to ensure the global alpha level was maintained). The original sample size calculation was as follows: A sample size of approximately 610 patients in total using a 1:1 randomisation ratio would provide at least 90% power to detect a hazard ratio of 1.7 in time to recovery. This sample size was calculated using a global two-sided alpha level of 0.05 and allowed for an interim analysis to assess futility. This sample size assumed a recovery rate in the placebo treatment arm of 29% at Day 28 and a dropout rate of 25% spread uniformly over the 28-day study period. The daily assessment of COVID-19 symptoms and limitation of usual activities was added as a secondary endpoint. In addition, the World Health Organization (WHO) Ordinal Scale of Clinical Improvement (OSCI) assessments were to continue until Day 35 (instead of Day 28). Text was edited for clarity and consistency.	21 Dec 2020
3	An exclusion criterion that prevented patients who had a previous SARS-CoV-2 vaccination from taking part in the study was removed. Text was edited for clarity and consistency.	22 Feb 2021
4	Additional guidance was provided on conducting various assessments, the importance of maintaining contact with patients throughout the 90-day follow-up period was emphasised, and additional guidance on the role of the Independent Data Monitoring Committee/Data Safety Monitoring Committee was provided. Text was edited for clarity and consistency.	9 Sep 2021

Inclusion criteria

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

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

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

4. Required oxygen therapy via nasal prongs or mask (WHO OSCI score of 4).
5. Provided informed consent.
6. Female patients were ≥1 year post-menopausal, surgically sterile, or using a defined highly effective method of contraception.
7. Women not of childbearing potential were defined as women either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who were postmenopausal.

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

Exclusion Criteria

1. Evidence of ongoing SARS-CoV-2 infection for more than three weeks, confirmed by a validated molecular assay or validated antigen assay.

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

WHO OCSI

The WHO OSCI is a nine-point scale (0, no clinical or virological evidence of infection; 8, death) as described in the February 2020 WHO R&D Blueprint for Novel Coronavirus [1], and was assessed either face-to-face or by telephone/video link by a clinically qualified member of the study team.

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

To allow a consistent approach to the OSCI assessment for patients that were discharged from hospital, on the day of hospital discharge and on the days following hospital discharge patients were asked the following questions about their clinical status and return to the pre-COVID-19 level of activity:

- “In the past 24 hours, did you experience any signs or symptoms of your coronavirus infection?” (Yes/No)
- “In the past 24 hours, did you feel that your usual activities (e.g. work, study, housework, family or leisure activities) have returned to the level from before your coronavirus infection and did not require additional assistance/support*?” (Yes/No)

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

To minimise any potential influence on the patients, trial staff read the questions to patients verbatim. The below scoring algorithm was applied.

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

BCSS

Patients were asked by trained staff to report the severity of breathlessness, cough and sputum symptoms, each on a five-point scale with higher scores indicating more severe symptoms [2].

1. How much difficulty did you have breathing today?
    - 0 = None – unaware of any difficulty
    - 1 = Mild – noticeable when performing strenuous activity (e.g. running)
    - 2 = Moderate – noticeable even when performing light activity (e.g. bedmaking or carrying groceries)
    - 3 = Marked – noticeable when washing or dressing
    - 4 = Severe – almost constant, present even when resting
2. How was your cough today?
    - 0 = No cough – unaware of coughing
    - 1 = Rare – cough now and then
    - 2 = Occasional – less than hourly
    - 3 = Frequent – one or more times an hour
    - 4 = Almost constant – never free of cough or need to cough
3. How much trouble did you have due to sputum today?
    - 0 = None – unaware of any trouble
    - 1 = Mild – rarely caused trouble
    - 2 = Moderate – noticeable trouble
    - 3 = Marked – caused a great deal of trouble
    - 4 = Severe – almost constant trouble

NEWS2

NEWS2 is a tool developed by the Royal College of Physicians that aggregates physiological measurements which are already recorded in routine practice [3]. The highest NEWS2 score for each calendar day was collected; data were not recorded after discharge.

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

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

COVID-19 symptom assessment

Fever/feeling feverish	◯ Yes	◯ No	Wheezing	◯ Yes	◯ No
Cough	◯ Yes	◯ No	Chest Pain	◯ Yes	◯ No
Cough with sputum	◯ Yes	◯ No	Muscle aches (myalgia)	◯ Yes	◯ No
Cough with bloody sputum/haemoptysis	◯ Yes	◯ No	Joint pain (athralgia)	◯ Yes	◯ No
Sore throat	◯ Yes	◯ No	Fatigue/ malaise	◯ Yes	◯ No
Runny nose (rhinorrhoea)	◯ Yes	◯ No	Shortness of Breath (dysponea)	◯ Yes	◯ No
Ear pain	◯ Yes	◯ No	Loss of smell and/or taste	◯ Yes	◯ No
Headache	◯ Yes	◯ No	Vomiting/nausea	◯ Yes	◯ No
Other	◯ Yes	◯ No			

If 'other', specify here:

Statistical methods

Covariate-adjusted differences in proportions were derived from the logistic model estimates, and were formally assessed for statistical significance with a gatekeeping strategy. The proportions of patients recovering, or discharged from hospital were assessed using logistic regression models, and the improvement in OSCI score was assessed using ordinal logistic regression models. The change in BCSS was assessed using mixed models for repeated measures (MMRM). All other secondary endpoints were summarised descriptively only. For the handling of missing data see the supplement.

For the primary endpoints, patients who died were censored at 28 days, the maximum time to event allowed by the study design (note that as hospital discharge or recovery had to be sustained for at least 7 days, the latest timepoint at which a patient could be discharged or recover to be considered in the primary endpoints was Day 28). For analyses using the WHO OSCI, including the primary and key secondary endpoints, patients with a WHO OSCI score of 8, indicating death, had subsequent missing WHO OSCI assessments imputed as 8. In addition, if other data sources such as adverse events indicated a patient died, all missing WHO OSCI scores on and after the date of death were imputed as 8. Other missed OSCI assessments were not imputed for the primary endpoints, but hospital discharge was confirmed by the patient's location, and recovery was only confirmed if sufficient non-missing data were available. Patients who could not be confirmed as discharged/recovered or who withdrew from the study within 7 days of the event were treated as censored at the date last known to be hospitalised/not recovered. Key secondary endpoints were derived using observed data. For BCSS, missing breathless scores were imputed as 4 if the WHO OSCI score at the corresponding visit was ≥5, with cough and sputum scores considered missing at random and total scores calculated by summing the imputed symptom scores, where possible. Missing breathlessness, cough and sputum scores at all other visits were considered missing at random and were imputed, but were accounted for by the MMRM analysis.

Results

Table S2. Reasons for exclusion from the per-protocol population.

Reason	Treatment group	
	Placebo	SNG001
Clinical practice had a potential impact on efficacy assessment	1	1
Patient or relatives declined advanced respiratory support	0	3
Failed to receive two full doses of study medication in the first three days of treatment	36	31
Discharged from hospital for reason other than severity of condition	15	16
No positive SARS-CoV-2 result	0	1
Patient first reported symptoms more than three weeks prior to randomisation	1	0
Received study medication that was outside of temperature range	0	1

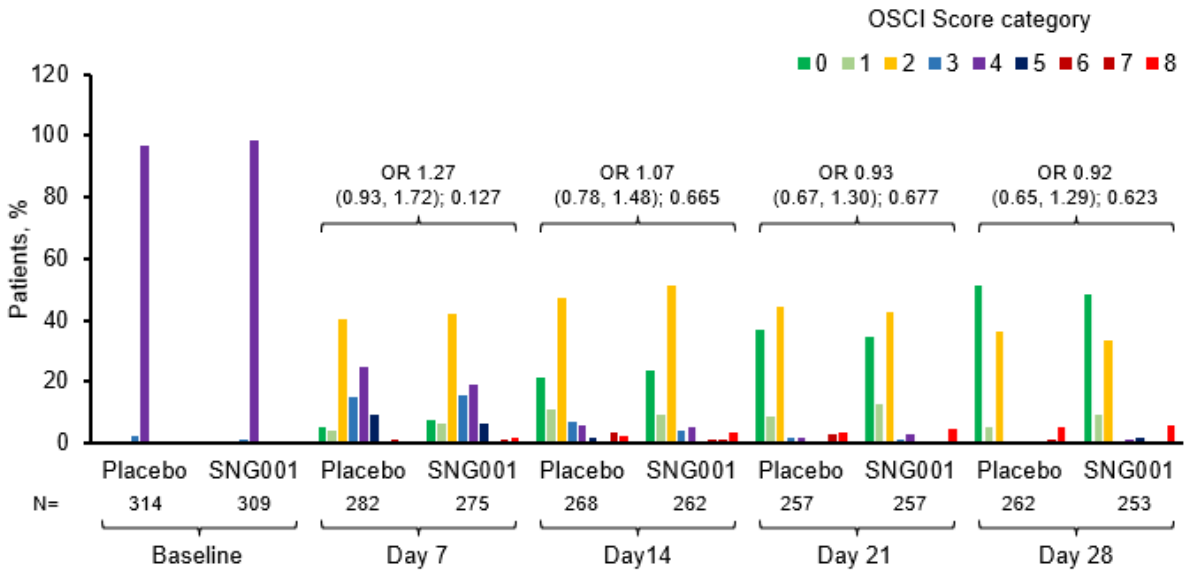
Table S3. Proportions of patients recovering or discharged from hospital, and changes from baseline in BCSS score (intention-to-treat population).

Parameter	Placebo plus SoC (N=314)	SNG001 plus SoC (N=309)	SNG001 vs placebo difference
Patients recovering (WHO OSCI score ≤1 sustained for ≥7 days)			
At Day 7	17 (5.4%)	28 (9.1%)	1.71 (0.90, 3.22); 0.101
At Day 14	73 (23.2%)	75 (24.3%)	0.99 (0.67, 1.45); 0.942
At Day 21	118 (37.6%)	117 (37.9%)	0.96 (0.68, 1.35); 0.824
At Day 28	151 (48.1%)	145 (46.9%)	0.92 (0.66, 1.28); 0.613
Patients discharged from hospital			
At Day 7	141 (44.9%)	154 (49.8%)	1.18 (0.85, 1.64); 0.323
At Day 14	223 (71.0%)	231 (74.8%)	1.17 (0.81, 1.70); 0.406
At Day 21	249 (79.3%)	245 (79.3%)	0.96 (0.64, 1.43); 0.828
At Day 28	255 (81.2%)	249 (80.6%)	0.92 (0.61, 1.40); 0.706
Change from baseline in BCSS total score			
At Day 7	–2.2 (–2.4, –2.0)	–2.1 (–2.3, –1.9)	0.1 (–0.3, 0.4); 0.726
At Day 14	–3.0 (–3.2, –2.8)	–2.9 (–3.1, –2.6)	0.2 (–0.2, 0.5); 0.354
Days 2–15	–2.2 (–2.4, –2.1)	–2.1 (–2.3, –2.0)	0.1 (–0.1, 0.3); 0.410
Change from baseline in BCSS breathlessness score			
At Day 7	–0.71 (–0.83, –0.59)	–0.75 (–0.88, –0.63)	–0.04 (–0.22, 0.13); 0.627
At Day 14	–0.99 (–1.12, –0.86)	–1.03 (–1.16, –0.91)	–0.04 (–0.22, 0.14); 0.635
Days 2–15	–0.75 (–0.85, –0.65)	–0.78 (–0.87, –0.68)	–0.03 (–0.17, 0.11); 0.699
Change from baseline in BCSS cough score			
At Day 7	–0.93 (–1.03, –0.82)	–0.84 (–0.94, –0.73)	0.09 (–0.06, 0.24); 0.255
At Day 14	–1.31 (–1.42, –1.21)	–1.17 (–1.28, –1.07)	0.14 (–0.01, 0.29); 0.065
Days 2–15	–0.93 (–1.01, –0.86)	–0.84 (–0.91, –0.76)	0.10 (–0.01, 0.20); 0.063
Change from baseline in BCSS sputum score			
At Day 7	–0.44 (–0.52, –0.37)	–0.43 (–0.50, –0.35)	0.02 (–0.09, 0.12); 0.757

Parameter	Placebo plus SoC (N=314)	SNG001 plus SoC (N=309)	SNG001 vs placebo difference
At Day 14	–0.60 (–0.67, –0.53)	–0.56 (–0.63, –0.48)	0.05 (–0.06, 0.15); 0.377
Days 2–15	–0.46 (–0.51, –0.40)	–0.42 (–0.48, –0.37)	0.04 (–0.04, 0.11); 0.350

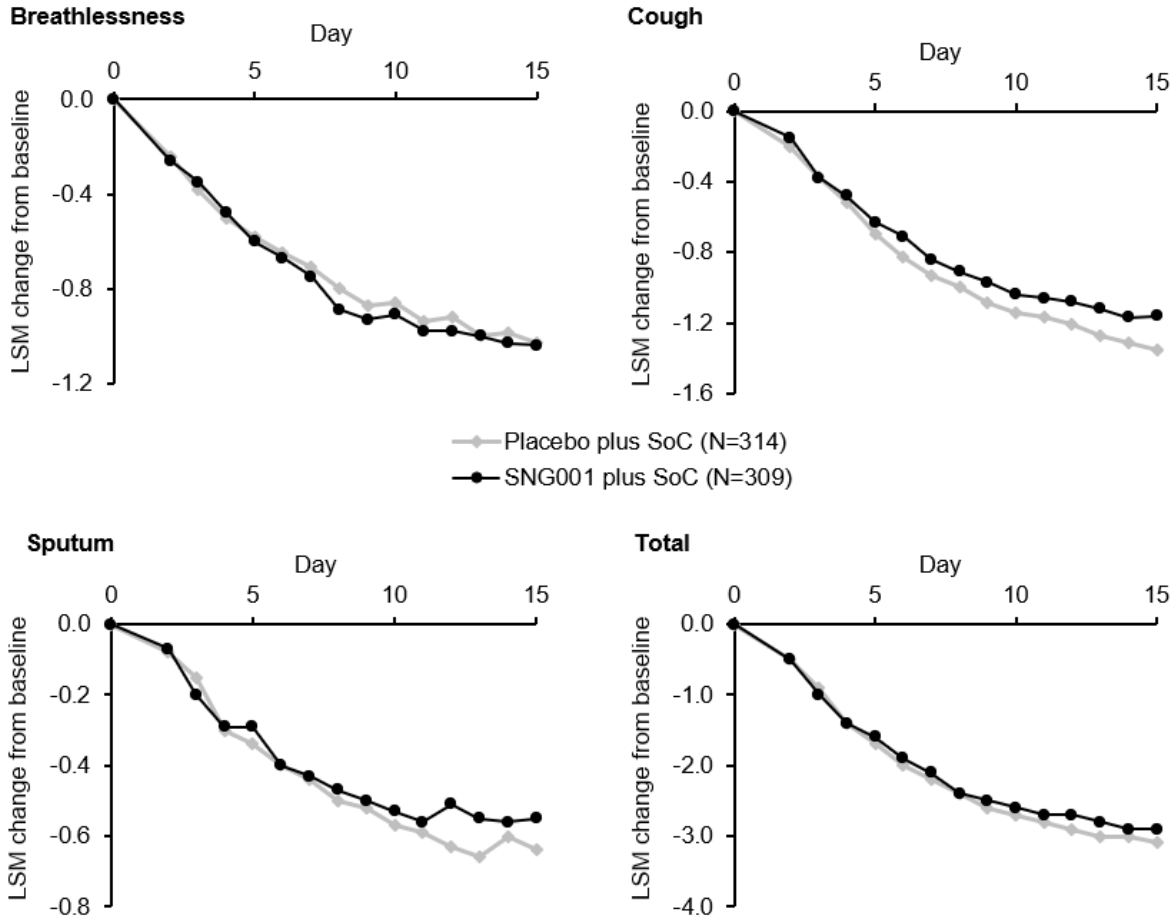
Treatment group data are number of patients (%) or least squares mean (95% confidence interval). SNG001 vs placebo differences are odds ratio (95% CI); p value, except for BCSS endpoints, which are least squares mean (95% confidence interval); p value. SoC, standard of care; WHO OSCI, World Health Organization Ordinal Scale of Clinical Improvement; BCSS, Breathlessness, Cough and Sputum Scale.

Figure S1. Patients categorised by WHO OSCI score at baseline and Days 7, 14, 21 and 28, with odds ratio for a better outcome (intention-to-treat population).



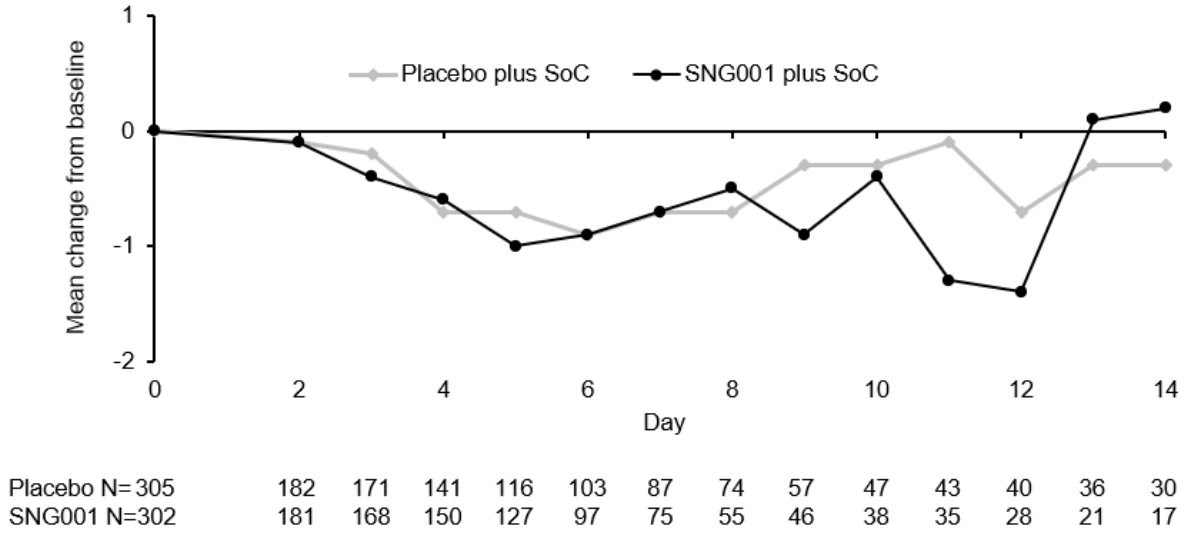
WHO OSCI, World Health Organization Ordinal Scale of Clinical Improvement (0 = No clinical or virological evidence of infection; 1 = No limitation of activities; 2 = Limitation of activities; 3 = Hospitalised – no oxygen therapy; 4 = Oxygen by mask or nasal prongs; 5 = Non-invasive ventilation, or high flow oxygen; 6 = Intubation and mechanical ventilation; 7 = Ventilation plus additional organ support; 8 = Death); OR, odds ratio.

Figure S2. Change from baseline in Breathlessness, Cough and Sputum Scale.



SoC, standard of care; LSM, least squares mean.

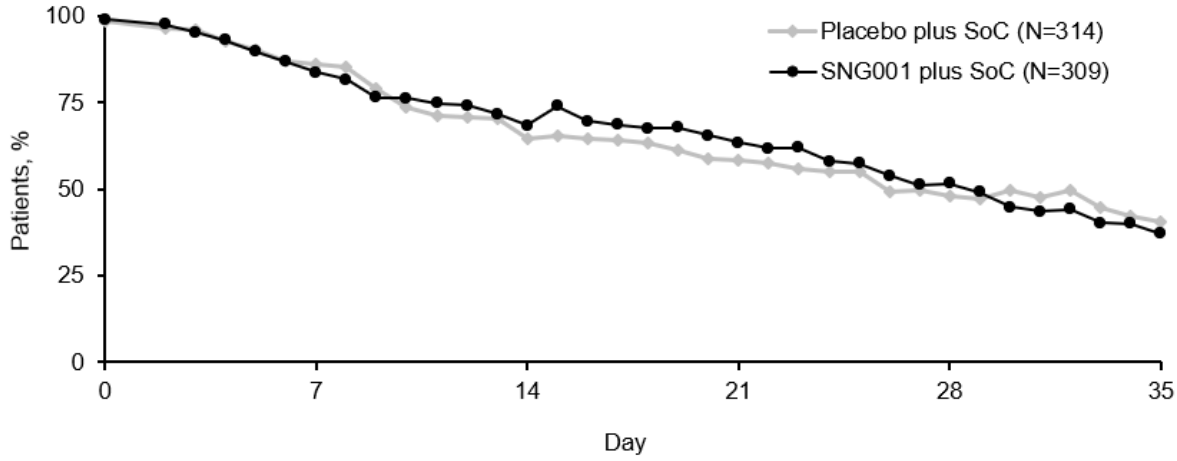
Figure S3. Mean change from baseline in National Early Warning System-2 score during the hospitalisation period.



Placebo N= 305	182	171	141	116	103	87	74	57	47	43	40	36	30
SNG001 N=302	181	168	150	127	97	75	55	46	38	35	28	21	17

Note: Data are presented up to Day 14 only. After this timepoint, too few patients have available data for meaningful interpretation of the results (mainly due to hospital discharge). SoC, standard of care.

Figure S4. Proportion of patients with any COVID-19 related symptom.



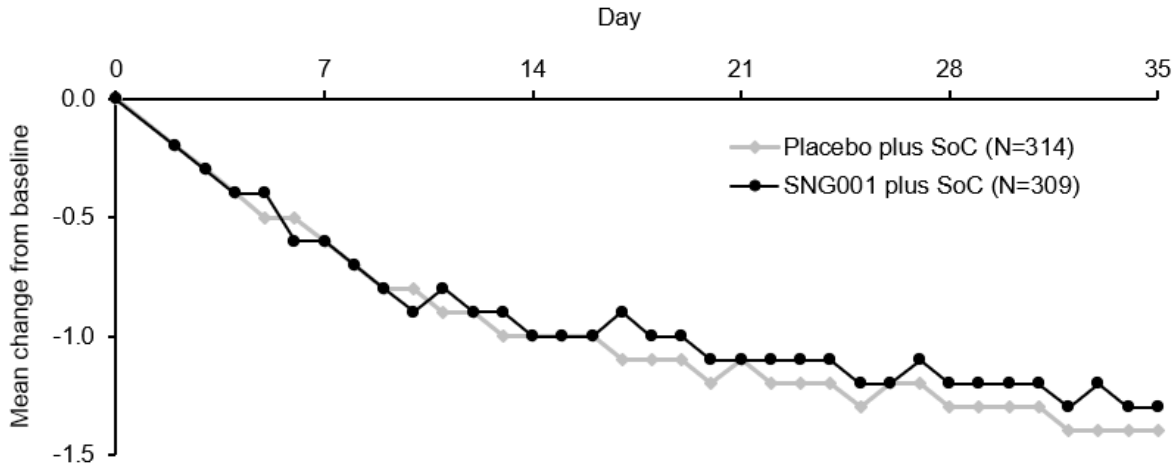
SoC, standard of care.

Table S4. EuroQol 5-dimension 5-level change from baseline (intention-to-treat population).

Parameter	Placebo plus SoC (N=314)	SNG001 plus SoC (N=309)
UK Crosswalk Index		
At Day 7	0.14 (0.293)	0.14 (0.267)
At Day 15 (end of treatment)	0.21 (0.288)	0.24 (0.253)
At Day 28 (follow-up)	0.28 (0.282)	0.26 (0.266)
Visual analogue scale		
At Day 7	13.1 (18.53)	15.8 (19.96)
At Day 15 (end of treatment)	20.9 (19.17)	22.8 (19.87)
At Day 28 (follow-up)	24.8 (20.84)	26.7 (20.26)

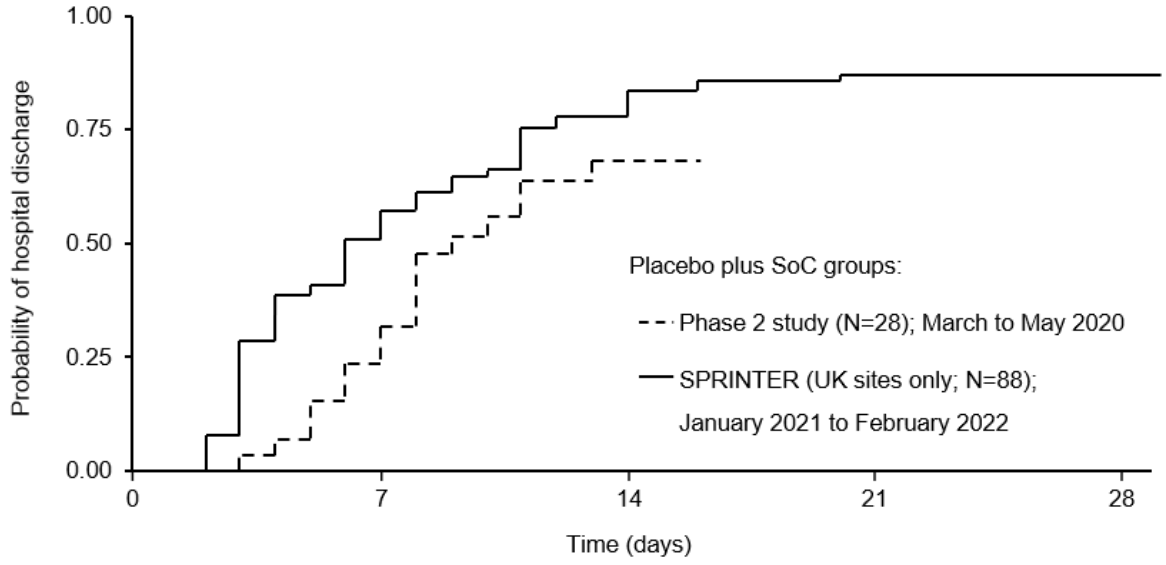
Data are mean (standard deviation). SoC, standard of care.

Figure S5. Mean change from baseline in EuroQol 5-dimension 5-level usual activities subscale.



SoC, standard of care.

Figure S6. Time to hospital discharge in the placebo plus standard of care groups in UK sites of the current study, and in the previous Phase II study.



SoC, standard of care.

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2. Leidy NK, Rennard SI, Schmier J, Jones MKC, Goldman M. The Breathlessness, Cough, and Sputum Scale. The development of empirically based guidelines for interpretation. Chest 2003; 124: 2182–2191.
3. Royal College of Physicians. National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. Updated report of a working party. 2017.