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

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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

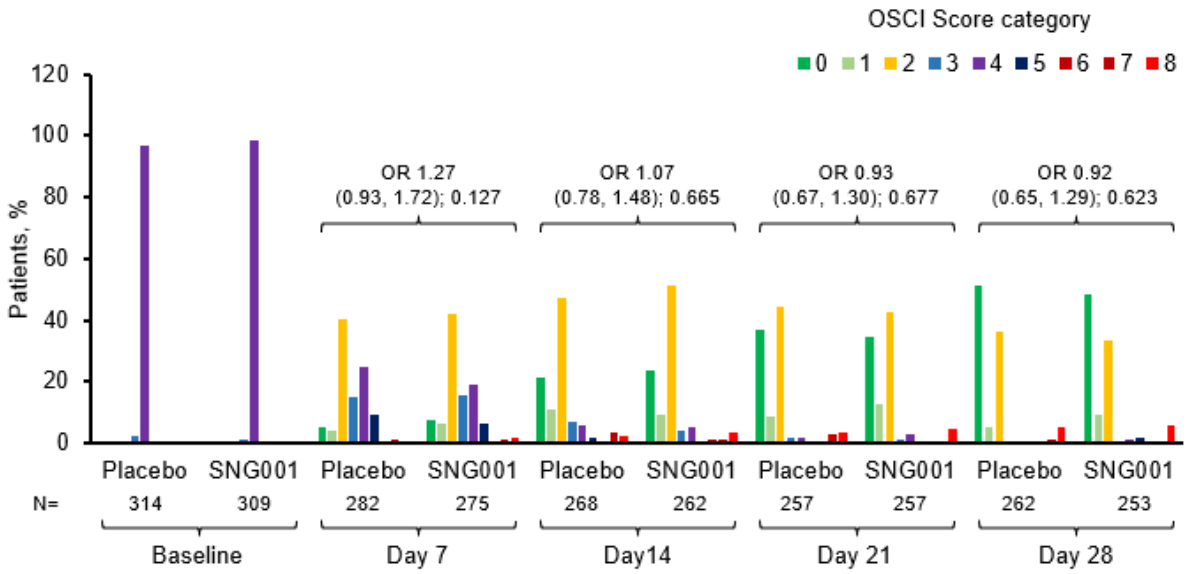
Table S3. Proportions of patients recovering or discharged from hospital, and changes from baseline in BCSS score (intention-to-treat population).

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

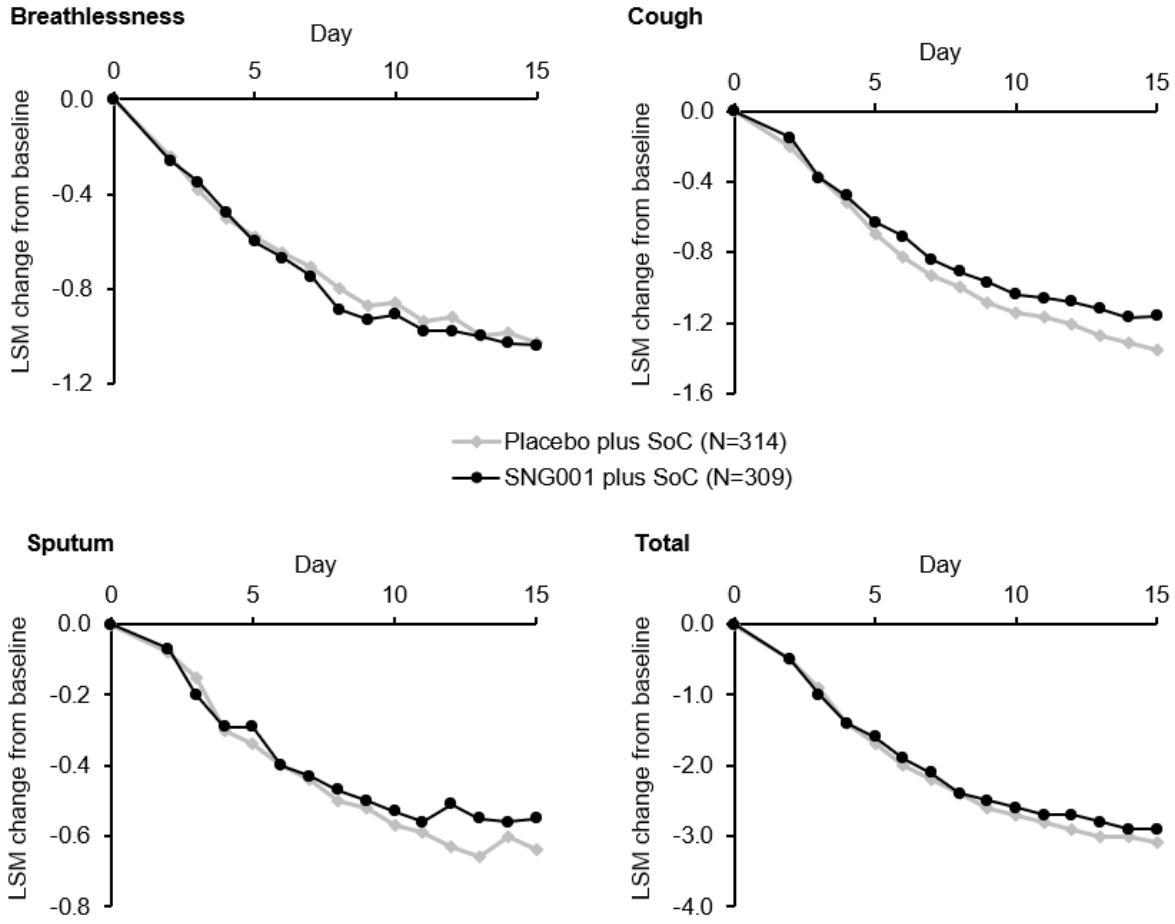
Treatment group data are number of patients (%) or least squares mean (95% confidence interval). SNG001 vs placebo differences are odds ratio (95% CI); p value, except for BCSS endpoints, which are least squares mean (95% confidence interval); p value. SoC, standard of care; WHO OSCI, World Health Organization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



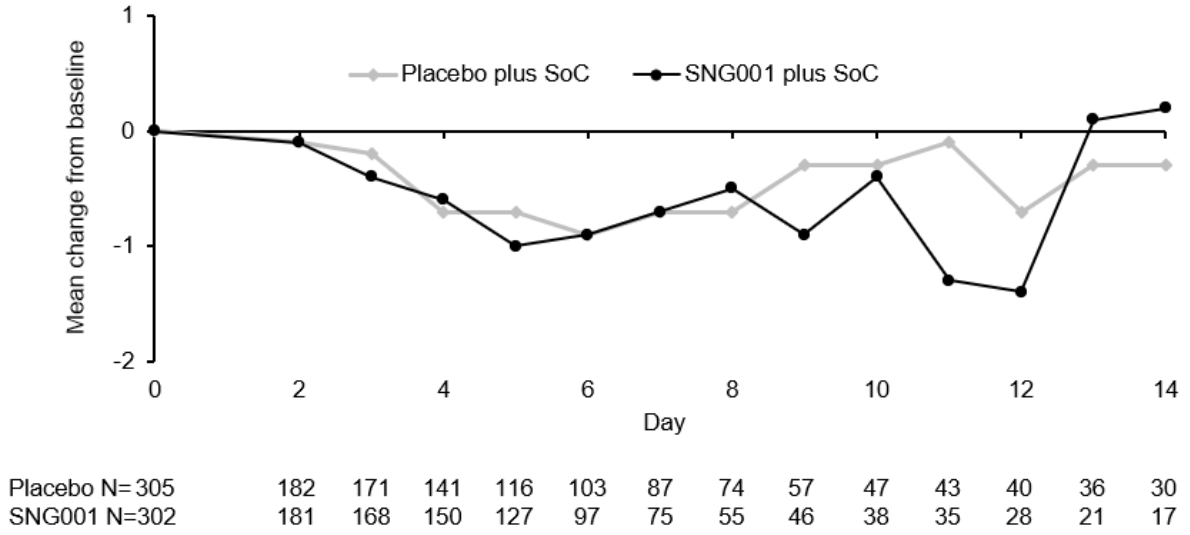
WHO OSCI, World Health Organization Ordinal Scale of Clinical Improvement (0 = No clinical or virological evidence of infection; 1 = No limitation of activities; 2 = Limitation of activities; 3 = Hospitalised – no oxygen therapy; 4 = Oxygen by mask or nasal prongs; 5 = Non-invasive ventilation, or high 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.

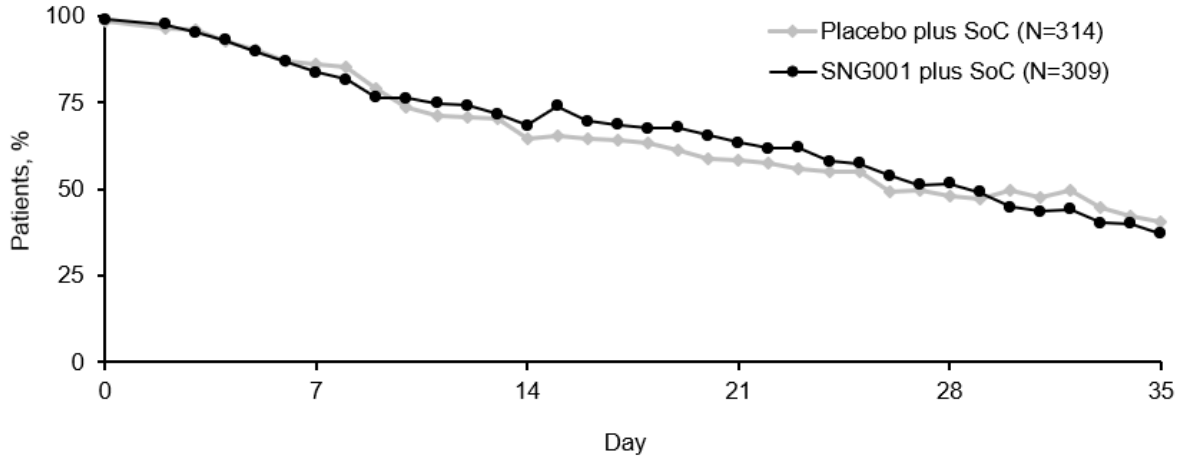
Figure S3. Mean change from baseline in National Early Warning System-2 score during the hospitalisation period.



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.



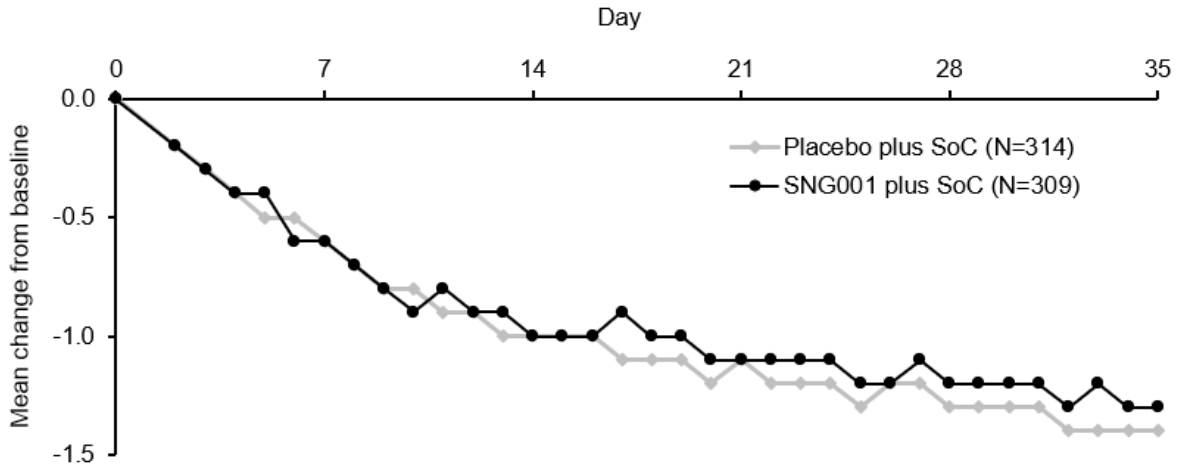
SoC, standard of care.

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)

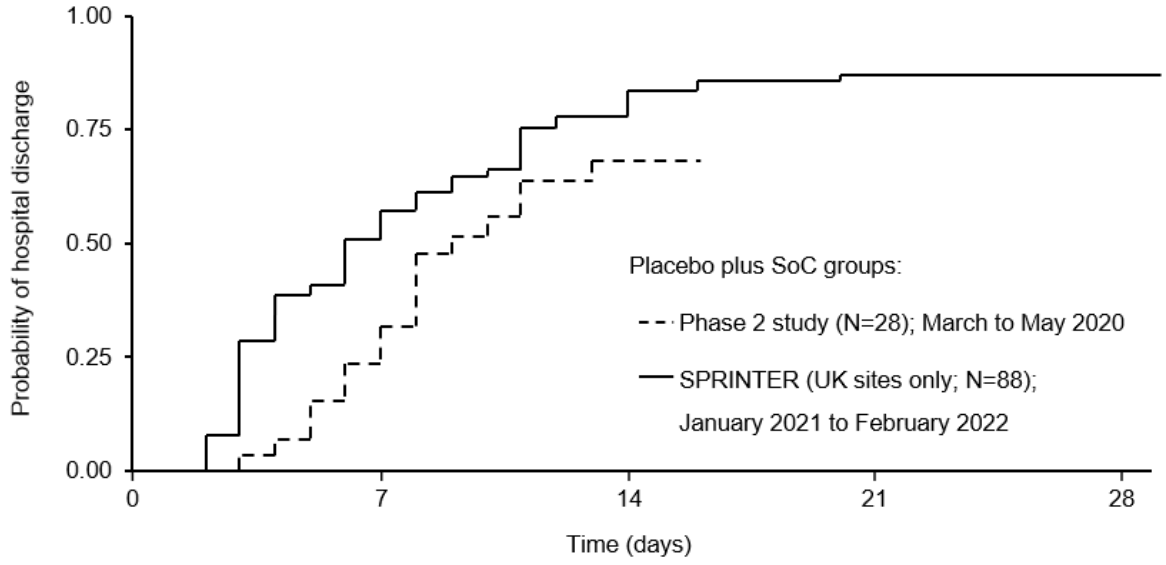
Data are mean (standard deviation). SoC, standard of care.

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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