



Nafamostat in hospitalized patients with moderate to severe COVID-19 pneumonia: a randomised Phase II clinical trial

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ABSTRACT

Background: Nafamostat, a serine protease inhibitor, has been used for the treatment of disseminated intravascular coagulation and pancreatitis. In vitro studies and clinical reports suggest its beneficial effect in the treatment of COVID-19 pneumonia.

Methods: This phase 2 open-label, randomised, multicentre, controlled trial evaluated nafamostat (4.8 mg/kg/day) plus standard-of-care (SOC) in hospitalised patients with COVID-19 pneumonia (i.e., those requiring nasal high-flow oxygen therapy and/or non-invasive mechanical ventilation). The primary outcome was the time to clinical improvement. Key secondary outcomes included the time to recovery, rates of recovery and National Early Warning Score (NEWS). The trial is registered with ClinicalTrials.gov Identifier: NCT04623021.

Findings: A total of 104 patients, mean age 58.6 years were enrolled in 13 clinical centres in Russia between 25/9/2020 and 14/11/2020 and randomised to nafamostat plus SOC (n=53) or SOC alone (n=51). There was no significant difference in time to clinical improvement (primary endpoint) between the nafamostat and SOC groups (median 11 [interquartile range (IQR) 9 to 14] vs 11 [IQR 9 to 14] days; Rate Ratio [RR; the ratio for clinical improvement], 1.00; 95% CI, 0.65 to 1.57; p=0.953). In 36 patients with baseline NEWS ≥ 7 , nafamostat was superior to SOC alone in median time to clinical improvement (11 vs 14 days; RR, 2.89; 95% CI, 1.17 to 7.14; p=0.012). Patients receiving nafamostat in this subgroup had a significantly higher recovery rate compared with SOC alone (61.1% (11/18) vs 11.1% (2/18) by Day 11, p=0.002). The 28-day mortality was 1.9% (1/52) for nafamostat and 8.0% (4/50) for SOC (95% CI, -17.0 to 3.4; p=0.155). No case of COVID-19 related serious adverse events leading to death was recorded in the patients receiving nafamostat.

Interpretation: Our study found no significant difference in time to clinical improvement between the nafamostat and SOC groups, but a shorter median time to clinical improvement in a small group of high-risk COVID-19 patients requiring oxygen treatment. To assess the efficacy further, a larger Phase 3 clinical trial is warranted.

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1. Introduction

The current Coronavirus disease 2019 (COVID-19) pandemic which emerged in China in late 2019 is caused by the novel

coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Covid-19 has caused considerable and widespread morbidity, mortality, and economic damage, and poses a serious threat to global public health [2,3]. Severe pneumonia requiring treatment with supplemental oxygen occurs in approximately 15% of adults with COVID-19, and a further 5% develop critical disease with hypoxic respiratory failure, acute respiratory distress syndrome, and multiorgan failure necessitating ventilator support [4, 5].

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Research in context

Evidence before this study

Nafamostat demonstrated antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *in vitro* and we evaluated its clinical potential in hospitalised patients with Coronavirus disease 2019 (COVID-19) pneumonia. We searched PubMed, up to June 30, 2021, for published clinical trials assessing the effect of nafamostat among patients with COVID-19. The search terms used were (“COVID-19” or “2019-nCoV” or “SARS-CoV-2”) AND “nafamostat” AND (“clinical trial” or randomised controlled trial”). We identified no published clinical trials of the effect of nafamostat in patients with COVID-19.

Added value of this study

Our study is the first randomised, clinical trial assessing the effect of intravenous nafamostat (infusion over 24 hours) plus standard of care (SOC) with SOC alone in hospitalized adult patients with COVID-19 pneumonia requiring supplemental oxygen. In the full analysis population, there was no significant difference in the primary endpoint (time to clinical improvement) between the 2 groups. However, in patients with a baseline National Early Warning Score (NEWS) ≥ 7 , nafamostat was superior to SOC alone in the time to clinical improvement (11 vs 14 days), and this subgroup had a significantly higher recovery rate and a lower mortality rate compared with SOC alone. No case of COVID-19 related adverse events leading to death was recorded in the patients receiving nafamostat.

Implications of all the available evidence

Our preliminary study suggests that nafamostat may be beneficial in the treatment of high-risk COVID-19 patients requiring oxygen treatment. Future studies involving nafamostat, including earlier treatment and larger numbers of patients, are supported by the findings of our exploratory study so as to help ascertain its potential clinical effectiveness in patients with COVID-19.

Nafamostat has been approved and registered for use as an anti-coagulant during hemodialysis in Japan and Korea for over 20 years [16–18] and it is reported to reduce disseminated intravascular coagulation in patients with hematological malignancies [19]. In *ex vivo* experiments, nafamostat inhibited complement activation and improved lung xenograft function [20]. Several clinical case reports also suggested that nafamostat treatment may be beneficial in patients with severe COVID-19 pneumonia [21,22].

Herein, we report the results of an open-label, randomised phase 2 trial which evaluated clinical course of hospitalised patients with confirmed COVID-19 pneumonia who received standard-of-care (SOC; including supplemental oxygen) with or without nafamostat.

2. Methods

2.1. Study design

This phase 2 open-label, randomised, multicentre, controlled trial was conducted in 13 study sites in one country, Russia, to evaluate the efficacy and safety of nafamostat (Nafabelltan, CKD-314, Chong Kun Dang Pharm, Korea) in hospitalized adult patients with COVID-19 -related pneumonia requiring supplemental oxygen treatment, nasal high-flow oxygen, or non-invasive mechanical ventilation [**but not including patients requiring invasive intubation or** extracorporeal membrane oxygenation (ECMO)]. Enrolment for the trial began on September 25, 2020 and ended on November 14, 2020. Eligible patients were randomly assigned in a 1:1 ratio to receive Standard of Care (SOC), either with or without nafamostat (4.8 mg/kg/day) via 24-hour intravenous infusion for 10 days or until hospital discharge.

Dose reduction was allowed by 0.1 mg/kg/hr (2.4 mg/kg/day) at the investigator's discretion as indicated by patient tolerability (e.g., hyperkalemia or hyponatremia). SOC was administered based on the Ministry of Health of the Russian Federation Interim Guidelines for the prevention, diagnosis and treatment of COVID-19 [24]. However, starting new antiviral or anti-inflammatory treatment after randomisation was not permitted, and only dose reductions or discontinuation were allowed. Glucocorticosteroid therapy was prohibited throughout the study.

Prior to the trial, written approval from the Independent Ethics Committees (IEC) of all study centres (see Supplementary Table 1 for study centre details) was obtained in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines and Eurasian Economic Union (EEU) principles, and in line with the Declaration of Helsinki, as well as applicable legislation and regulations of the Russian Federation. The following documents were required to be submitted for the IEC's review: study protocol with amendments, patient's information list and the informed consent form, written materials to be submitted to the patients, investigator's brochure, information of safety of the study drug application, information on payments and other remunerations to the patients, investigator's scientific biography and other documents at request. All subjects (or their legally authorized representatives) provided written informed consent. The trial is registered with ClinicalTrials.gov Identifier: NCT04623021.

2.2. Randomisation

Block randomisation was performed using a remote access Interactive Web Response System (IWRS), and was stratified according to disease severity [7-category ordinal scale (the COVID Outcomes Scale) recommended by the World Health Organization] and concomitant antiviral and/or anti-inflammatory medications [23,24]. For concomitant therapy, the following strata were used: (1) treatment with antiviral products only, (2) treatment with anti-inflammatory

Cellular entry of SARS-CoV-2 depends on two membrane-bound host proteases— angiotensin converting enzyme 2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2). The SARS-CoV-2 spike (S) glycoprotein protein binds to ACE2 which is activated following cleavage by TMPRSS2 [6]. The mesylate salt of nafamostat (INN nafamostat mesilate; henceforth called nafamostat) is a serine protease inhibitor and a potent inhibitor of SARS-CoV-2 activation *in vitro* [7,8]. Indeed, in a comparative *in vitro* study of drugs with antiviral activity against SARS-CoV-2 in human lung cells, nafamostat was more potent than 24 drugs with known antiviral activity such as chloroquine, lopinavir, and remdesivir [9,10].

There is an urgent unmet need for drugs to treat COVID-19 and repurposed drugs are an attractive option as their safety profile is well-established. Several repurposed drugs including chloroquine, hydroxychloroquine and lopinavir-ritonavir have produced disappointing results in COVID-19 [11–13]. However, based on favorable results in a large placebo-controlled phase 3 trial, remdesivir was approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized patients who require supplemental oxygen [14]. In addition, dexamethasone reduced 28-day mortality in patients hospitalized with COVID-19 receiving respiratory support (invasive mechanical ventilation or oxygen alone) and was approved by the European Medicines Agency (EMA) [15].

products only and (3) no treatment with antiviral and anti-inflammatory products [24].

2.3. Patients

Hospitalised patients aged ≥ 18 years with confirmed COVID-19 infection by RT-PCR of SARS-CoV-2 in a sample collected < 72 hours prior to randomisation; and newly diagnosed COVID-19 pneumonia by chest computed tomography (CT) scan or chest X-ray < 72 hours prior to randomisation were enrolled. Patients were required to have a score of 4 (hospitalisation, requiring supplemental oxygen) or 5 (hospitalisation, requiring nasal high-flow oxygen therapy and/or non-invasive mechanical ventilation) using the 7-category ordinal scale for clinical status.

Main exclusion criteria were patients requiring invasive mechanical ventilation and/or ECMO at screening; serious chronic disease with unstable disease status; active bleeding or any clinical condition deemed as high-risk for bleeding and a contraindication for anticoagulant treatment; pregnant or lactating females; hyperkalemia (serum potassium level > 5.1 mmol/L); moderate/severe liver disease (Child-Pugh score of B or C); ALT or AST levels > 5 -fold above the upper limit of normal (ULN); estimated glomerular filtration rate (eGFR) < 30 mL/min (including patients receiving hemodialysis or hemofiltration); abnormal ECG (QTcB or QTcF > 500 ms); medical history of clinically significant ventricular arrhythmias; rapidly deteriorating clinical condition or low likelihood of completing the study according to the investigator's opinion; hypersensitivity to the investigational drug; and clear evidence of secondary bacterial infection (diagnosed by laboratory tests and/or clinical examination).

2.4. Outcomes

The primary efficacy outcome was time to clinical improvement defined as the time from randomisation to either discharge from hospital or improvement of two points on the 7-category ordinal scale, whichever came first.

Secondary efficacy outcomes included time to recovery defined by either discharge from hospital or hospitalisation for infection-control purposes only (no longer requiring oxygen and medical care for COVID-19 pneumonia); the proportion of patients with recovery; rate of clinical improvement; changes of clinical status based on the 7-category ordinal scale; changes in the National Early Warning Score (NEWS) [25] at days 4, 7, 11 and 28; time to NEWS ≤ 2 which was maintained for 24 hours; changes in chest CT scan/X-ray; duration of hospitalisation; duration and incidence of oxygen treatment; and 28-day mortality. Exploratory virologic efficacy included proportion of negative PCR results and time to the first PCR negative result in two consecutive PCR tests.

Patients' clinical status was assessed daily during the treatment period and then on Days 14 and 28.

Safety outcomes included death up to Day 28, serious adverse events (SAEs) and Grade 3 and 4 AEs, discontinuation of study drug for any reason, and changes in laboratory values over time.

Safety outcomes was performed in all patients who started their assigned treatment (Safety Analysis Set; SAF) and efficacy outcome was performed in the Full Analysis Set (FAS) defined as all SAF patients who had a baseline and at least one post-dose ordinal scale result for the clinical status.

2.5. Statistical analysis

Power calculations showed that with 80% power, a two-sided type-I error rate of 5% and 66% overall probability of event occurrence, a total of 100 patients was needed for an improvement rate ratio (Hazard Ratio for clinical improvement calculated using the Cox proportional hazard model) of 2.0 in time to clinical improvement

(primary efficacy outcome). This value for improvement ratio is higher than that reported in the remdesivir phase 3 trial (1.32) which used time to improvement as the primary endpoint [14]. Stratified log-rank tests were used to compare differences between treatment arms in attainment of clinical improvement in the Full Analysis Set (FAS) and subgroups with stratification by disease severity and concomitant SOC. Rate ratio (RR) with 95% confidence intervals (CI) for time to event outcomes was derived from Cox proportional hazard model with treatment as a fixed factor. For time-to-recovery and time-to-improvement analyses, data for patients who did not recover were censored at the date of early discontinuation, and data for patients who died were censored at Day 28.

For secondary endpoints, comparisons of frequencies and categorical data between groups were performed using χ^2 or Fisher's exact test, and continuous data using Mann-Whitney's nonparametric test or Student's *t*-test. Confidence intervals calculated for change in clinical improvement were not corrected for multiple testing. In addition to the populations defined for stratification (disease severity and concomitant standard care), subpopulation analyses included age ≥ 65 years, hypoxemia (SpO₂ $< 90\%$) and patients with a poor outcome risk (NEWS ≥ 7 and NEWS ≥ 6).

An interim analysis was performed by the Data Safety Monitoring Board (DSMB) when 50% of patients completed treatment to review safety data (e.g., SAEs, grade 3-4 AEs, discontinuations, and deaths) and insufficient efficacy for the purpose of recommendation of study continuation or not.

2.6. Role of the funding source

The trial was designed and conducted by the sponsor (CKD) in collaboration with the principal investigators and in accordance with the protocol and amendments. The sponsor was responsible for the collection, analysis, and interpretation of the data, and the management of clinical trial and the manuscript preparation. Interpretation of the clinical findings was undertaken by the principal authors led by the corresponding author. All authors had full access to all clinical data and agreed with the final decision to submit for publication. As a national research project on COVID-19, this study was partially funded by National Research Foundation of Korea/Korea Research Institute of Bioscience and Biotechnology. However, they were not involved in the study design, operation, statistical analysis or interpretation of the results.

3. Results

3.1. Patients

A total of 108 patients were screened, of whom 104 were randomised to receive nafamostat plus SOC (nafamostat group; $n=53$) or receive standard of care alone (SOC group; $n=51$). One patient randomised to nafamostat did not receive any medication, and one patient in the SOC group did not have a post-baseline 7-point ordinal scale score. Consequently, the Full Analysis Set (FAS) comprised 52 and 50 patients in the nafamostat and SOC groups, respectively; and the Safety Analysis Set (SAF), 52 and 51 patients, respectively. Overall, 90.6% (48/53) of the nafamostat group and 78.4% (40/51) of the SOC group completed the study. Withdrawal due to AEs or serious AEs occurred in 3.8% (2/52) of the nafamostat group and 2.0% (1/51) of the SOC group (Figure 1).

The mean age of patients was 58.6 years and 49.5% (51/103) were male. All of the patients were Caucasian. Most patients had either one (39.8%; 41/103) or two or more (33.0%; 34/103) underlying conditions at enrolment; most commonly hypertension (62.1%), obesity (25.2%), and type 2 diabetes mellitus (10.7%). The median duration between symptom onset and randomization was 10 days (interquartile range, 8 to 12 days). Baseline ordinal score was 4 in 91.3% (94/

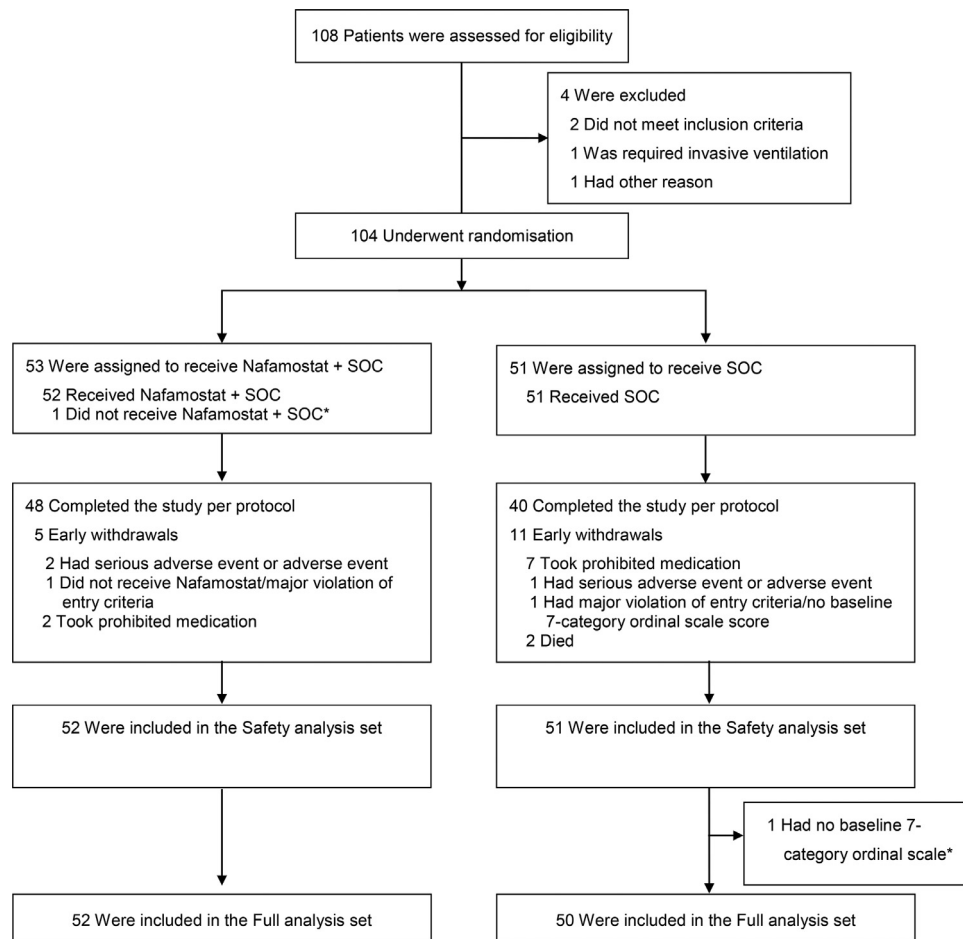


Fig. 1. Trial profile.

103), and 5 in 8.7% (9/103). Of the 9 patients with ordinal score 5, 6 were in the nafamostat group and 3 in the SOC group. The Mean NEWS scale score was 5.9 in the overall patient population and 35.9% (37/103) had NEWS 7 or higher. Mean CRP was 78.7 mg/L (Table 1). The standard concomitant medications used in the trial are shown in Supplementary Table 2.

3.2. Efficacy outcomes

3.2.1. Primary efficacy outcome/endpoint

There was no significant difference in time to clinical improvement between the two groups (median 11 vs 11 days; Rate Ratio [RR; the ratio for clinical improvement], 1.00; 95% CI, 0.65 to 1.57; $p=0.953$) (Table 2, Figure 2A, Figure 3A).

In patients with baseline NEWS ≥ 7 , time to clinical improvement was faster in the nafamostat group than the SOC group (median 11 vs 14 days; RR, 2.89; 95% CI, 1.17 to 7.14; $p=0.012$). Furthermore, the time to clinical improvement was numerically shorter in the nafamostat group than the SOC group in patients aged ≥ 65 years (median 11 vs 14 days; RR, 1.96; 95% CI, 0.86 to 4.47; $p=0.083$) as well as in the patients with a baseline SpO₂ $< 90\%$ (median 11 vs 14 days; RR, 2.56; 95% CI, 0.62 to 10.6; $p=0.190$) (Table 2, Figure 2, Figure 3A, Supplementary Figure 1). Changes with respect to the sub-groups NEWS < 7 , NEWS < 6 and age < 65 years demonstrated numerically lower but not statistically significant RRs for clinical improvement in the nafamostat + SOC and SOC groups, with a small improvement noted in NEWS grades after 11 days in the nafamostat + SOC group (change -5.0 vs. -3.6 in the SOC group; $p=0.036$) [Supplementary Table 3].

To compare the relative merits of treatment in patient with NEWS ≥ 7 vs. those with NEWS < 7 , a Cox proportional model for time to event outcomes and linear regression for continuous outcome was performed in the nafamostat + SOC vs. SOC groups (Supplementary Table 4). The results of this analysis highlighted benefit in patients with NEWS ≥ 7 and a significant interaction was shown between treatment group and NEWS grade in terms of clinical improvement ($p=0.005$), recovery ($p=0.002$), change in NEWS grades ($p=0.002$) and CRP levels ($p=0.036$).

The time to clinical improvement by randomisation strata including 7-ordinal scale score and concomitant standard treatment in the overall FAS was not different between the two groups (Supplementary Table 5).

3.2.2. Key secondary efficacy outcomes/endpoints

No significant difference was observed between the nafamostat group and SOC group in the time to recovery (median 11 vs 11 days; RR, 0.98; 95% CI, 0.62 to 1.55; $p=0.968$) as well as in the response rates of recovery (88.5% vs 80.0%) (Table 2, Figure 3B).

In patients with baseline NEWS ≥ 7 , the time to recovery was more rapid in the nafamostat group than the SOC group (10 vs 14 days; RR, 3.10; 95% CI, 1.19 to 8.06; $p=0.012$). The overall recovery rates were 94.4% vs 61.1%, respectively, and the rates by Day 11 were 61.1% vs 11.1% ($p=0.002$), respectively. The response rates for clinical improvement were the same as the recovery rates (Table 2, Figure 3). Furthermore, patients receiving nafamostat with a baseline NEWS ≥ 7 achieved a significant reduction in NEWS score, from 7.4 at baseline to 0.7 by day 11. On the other hand, the means NEWS score in the SOC group was 7.7 and decreased to 4.2 by day 11 (Table 2,

Table 1
Demographic and baseline characteristics of randomly assigned participants by study group.

Parameter	Nafamostat (N = 52)	SOC (N = 51)	Overall (N = 103)
Age (years)			
Mean (SD)	60.9 (12.3)	56.2 (12.7)	58.6 (12.6)
18–44, no. (%)	5 (9.6)	9 (17.6)	14 (13.6)
45–59, no. (%)	16 (30.8)	21 (41.2)	37 (35.9)
≥ 60, no. (%)	31 (59.6)	21 (41.2)	52 (50.5)
Male, n (%)	26 (50.0)	25 (49.0)	51 (49.5)
Race: Caucasian, no. (%)	52 (100.0)	51 (100.0)	103 (100.0)
Body weight (kg), Mean (SD)	90.5 (14.9)	90.6 (19.0)	90.5 (17.0)
Comorbidities, no. (%)			
None	13 (25.0)	15 (29.4)	28 (27.2)
One	20 (38.5)	21 (41.2)	41 (39.8)
Two or more	19 (36.5)	15 (29.4)	34 (33.0)
Median duration of symptom prior to randomisation (days), (IQR)	10.0 (8.0–12.0)	9.0 (7.0–11.0)	10.0 (8.0–12.0)
Median duration of hospitalisation prior to randomisation (days), (IQR)	2.0 (2.0–3.0)	2.0 (1.0–2.5)	2.0 (2.0–3.0)
Clinical status (7-category ordinal scale), n (%)			
4	46 (88.5)	48 (94.1)	94 (91.3)
5	6 (11.5)	3 (5.9)	9 (8.7)
National Early Warning Score (NEWS) score			
Mean (SD)	5.9 (1.4)	5.8 (1.8)	5.9 (1.6)
≥ 7, no. (%)	18 (34.6)	19 (37.3)	37 (35.9)
CRP (mg/L), Mean (SD)	80.0 (64.9)	77.5 (59.4)	78.7 (61.9)
Underlying condition, no. (%)			
Hypertension	35 (67.3)	29 (56.9)	64 (62.1)
Obesity	12 (23.1)	14 (27.5)	26 (25.2)
Type 2 diabetes mellitus	7 (13.5)	4 (7.8)	11 (10.7)
Concomitant medication, no. (%)			
Antiviral	35 (67.3)	29 (56.9)	64 (62.1)
Hydroxychloroquine	12 (23.1)	15 (29.4)	27 (26.2)
Azithromycin	14 (26.9)	11 (21.6)	25 (24.3)
Umifenovir	13 (25.0)	5 (9.8)	18 (17.5)
Favipiravir	7 (13.5)	7 (13.7)	14 (13.6)
Anti-inflammatory	6 (11.5)	11 (21.6)	17 (16.5)
Baricitinib	4 (7.7)	9 (17.6)	13 (12.6)
Olokizumab	1 (1.9)	3 (5.9)	4 (3.9)
Tocilizumab	1 (1.9)	1 (2.0)	2 (1.9)

IQR, interquartile range; SD, standard deviation

*intergroup comparison using Student's t-test or Mann-Whitney test

**intergroup comparison using the chi-squared test or Fisher's exact test

Supplementary Table 6, Supplementary Figure 2). Additional secondary endpoints improved in the nafamostat group included change in clinical status, time to sustained NEWS of 2 or lower, a shorter length of hospital stay, and 28-day mortality (Table 2).

3.3. Safety

Grade ≥3 AEs occurred in 5 patients (9.6%) in the nafamostat group and 8 patients (15.7%) in the SOC group (Table 3, Supplementary Table 7). The most common AEs associated with nafamostat were catheter site phlebitis (n = 7; 13.5%) vs 2 (3.9%) in the SOC group, hyponatremia (n = 4; 7.7%) vs 0, and respiratory failure (n = 3; 5.8%) vs 1 (2.0%). The most common AEs in the SOC group were dyspnea (n = 3; 5.9%) and pulmonary embolism (n = 2; 3.9%), neither of which were not recorded in the nafamostat group (Table 3).

A total of 5 patients reported serious AEs, 1 (1.9% of 52 patients) in the nafamostat group and 4 (7.8% of 51 patients) in the SOC group with fatal complications (Table 3, Supplementary Table 7). The patient in the nafamostat group experienced a grade 4 pneumothorax during installation of a subclavian catheter on Day 2 and discontinued the study. The patient was subsequently found to be HIV-positive (Day 4) and developed respiratory failure and multi-organ failure due to AIDS, and died on Day 22. No causality attributed to nafamostat was determined by the investigator. In the SOC group, four patients died;

2 (3.8%) from pulmonary embolism, 1 (2.0%) cardiac arrest, and 1 (2.0%) worsening respiratory failure.

Most AEs in the nafamostat group were mild in severity and no worsening of pneumonia symptoms or fatal outcome were reported (Table 3, Supplementary Table 7).

4. Discussion

This randomised clinical trial in hospitalized COVID-19 pneumonia showed that nafamostat treatment did not shorten the time to clinical improvement. However, in patients with baseline NEWS ≥7, compared to standard of care, nafamostat treatment shortened the time to clinical improvement by 3 days (11 vs 14 days; RR, 2.89; 95% CI: 1.17 to 7.14, p=0.012). In this subgroup, nafamostat treatment also shortened the time to recovery (i.e., no oxygen requirement nor medical care) by 4 days (10 vs 14 days; RR, 3.10; 95% CI: 1.19 to 8.06, p=0.012) and was associated with a trend of more rapid viral elimination (Supplementary Table 8). This is counterbalanced in the NEWS <7 and <6 groups in which clinical improvement and recovery was numerically higher in the SOC group, but it was not statistically significant.

The analysis with overall 103 patients showed that nafamostat was not superior to SOC alone in the primary outcome, time to clinical improvement (median 11 days vs 11 days; RR, 1.00 [95% CI: 0.65 to 1.57; p=0.953]). In patients with a baseline ordinal score of 5 (i.e., high-flow oxygen or non-invasive ventilation), time to clinical improvement favored nafamostat treatment (median 10 vs 16 days; RR 1.89 [95% CI: 0.21 to 17.26; p=0.582]), but the number of patients with baseline ordinal score 5 was too small (8.7%; 9/103).

The observed benefit of nafamostat was most evident in patients with a baseline NEWS ≥ 7. In this subgroup, nafamostat added to SOC showed 4-day faster recovery than SOC alone. Furthermore, 94.4% of patients receiving nafamostat recovered by day 28, compared to 61.1% of SOC alone. Time to NEWS normalisation (NEWS ≤2 which is maintained for 24 hours) was also 3 times faster in nafamostat group than the control group (RR, 3.11; 95% CI 1.31 to 7.38; p=0.007). In the Adaptive COVID-19 Treatment Trial (ACTT-1), the benefit of remdesivir was also most apparent in patients with a baseline ordinal score 5 (low-flow oxygen) [14].

Nafamostat has been used as an anticoagulant during hemodialysis in Korea and Japan for more than 2 decades, and its safety profile is well established. Of 3,602 patients treated with nafamostat, 7% reported side effects, including electrolyte disturbance (5.14%) such as hyperkalemia and hyponatremia, liver dysfunction (1.47%), hypersensitivity (0.3%), APTT abnormal extension (0.03%), thrombocytopenia (0.03%), and thrombocytosis (0.03%). In our clinical trial, it is of note that the most common AE was phlebitis (n=7; 13.5%) due to 24-hour intravenous infusion, and this led to discontinuation of the drug.

There are some limitations in this study that need to be considered when interpreting the results. Firstly, it was a phase 2 exploratory clinical trial and the number of patients was not sufficient to detect difference in clinical improvement, especially in the smaller subgroups. Although nafamostat exhibited beneficial effects in patients with a baseline NEWS ≥7, it is not certain that the same benefit will be achieved in patients with more severe disease or other risk factors such as older age or hypoxemia. Furthermore, in patients with less severe disease there was a tendency for patients with less severe disease (NEWS <6 and <7) to respond slightly more quickly with SOC than with nafamostat. The differences were not statistically significant and a larger study is required to clarify these differences.

The study was conducted in Russia, and SOC may differ in other countries. Furthermore, recommendations for treating COVID-19 have changed relatively quickly over time, and therefore the findings only apply to SOC when the trial was started. The patient population was stratified by SOC therapy, and a number of concomitant

Table 2
Outcomes overall and according to subgroups in full analysis set.

Outcome	Overall (N=102)		Age≥65 (N=36)		NEWS ≥ 6 (N = 60)		NEWS≥7 (N=36)	
	Nafamostat (n = 52)	SOC (n = 50)	Nafamostat (n = 22)	SOC (n = 14)	Nafamostat (n = 33)	SOC (n = 27)	Nafamostat (n = 18)	SOC (n = 18)
Clinical improvement								
No. of improvement	46 (88.5%)	40 (80.0%)	20 (90.9%)	11 (78.6%)	30 (90.9%)	20 (74.1%)	17 (94.4%)	11 (61.1%)
Time to clinical improvement (median, IQR)	11.0 (9.0-14.0)	11.0 (9.0-14.0)	11.0 (10.0-13.0)	14.0 (12.0-28.0)	11.0 (9.0-14.0)	13.5 (11.0-16.0)	11.0 (9.0-13.0)	14.0 (13.0-22.0)
Rate ratio (95% CI)	1.00 (0.65; 1.57 [p=0.953])		1.96 (0.86; 4.47 [p=0.083])		1.43 (0.79; 2.60 [p=0.189])		2.89 (1.17; 7.14 [p=0.012])	
No. of improvement by day 11	29 (55.8%)	23 (46.0%)	12 (54.5%)	3 (23.1%)	18 (54.5%)	7 (25.9%)	11 (61.1%)	2 (11.1%)
	p=0.324		p=0.049		p=0.025		p=0.002	
Recovery								
No. of recovery	46 (88.5%)	40 (80.0%)	20 (90.9%)	11 (78.6%)	30 (90.9%)	20 (74.1%)	17 (94.4%)	11 (61.1%)
Time to recovery (median, IQR)	11.0 (9.0-15.0)	11.0 (9.0-14.0)	11.0 (10.0-15.0)	14.0 (11.0-28.0)	11.0 (8.5-14.0)	13.5 (10.0-16.0)	10.0 (8.0-13.0)	14.0 (13.0-22.0)
Rate ratio (95% CI)	0.98 (0.62; 1.55 [p=0.968])		1.98 (0.86; 4.52 [p=0.087])		1.34 (0.74; 2.41 [p=0.314])		3.10 (1.19; 8.06 [p=0.012])	
No. of recovery by day 11	28 (53.8%)	25 (50.0%)	11 (50.0%)	4 (28.6%)	18 (54.5%)	7 (25.9%)	11 (61.1%)	2 (11.1%)
	p=0.698		p=0.204		p=0.025		p=0.002	
NEWS								
Baseline (mean±SD)	5.9±1.4	5.8±1.7	5.4±1.5	6.4±1.5	6.8±0.9	7.1±1.0	7.4±0.7	7.7±0.7
NEWS at day11 (Change from baseline), mean±SD	1.3±2.3 (-4.6±2.8)	2.2±3.0 (-3.6±2.7)	1.3±2.4 (-4.1±3.1)	2.8±3.0 (-3.6±3.0)	1.2±1.9 (-5.6±2.3)	3.3±3.4 (-3.9±3.2)	0.7±1.6 (-6.8±1.9)	4.2±3.5 (-3.5±3.6)
	p=0.054		p=0.621		p=0.018		p=0.002	
Time to NEWS≤2 maintained for 24hr (median, IQR)	10.0 (7.0-13.0)	9.0 (6.0-14.0)	10.0 (7.0-13.0)	14.0 (12.0-28.0)	10.0 (8.0-14.0)	14.0 (8.0-18.0)	10.0 (6.0-13.0)	14.0 (9.0-22.0)
Rate ratio	1.04 (0.68; 1.60 [p=0.843])		2.39 (1.10; 5.20 [p=0.021])		1.43 (0.81; 2.54 [p=0.222])		3.11 (1.31; 7.38 [p=0.007])	
Hospitalisation								
Duration of hospitalization (median, IQR)	11.0 (10.0-14.0)	11.0 (9.0-13.8)	11.0 (10.0-14.0)	13.0 (11.5-25.5)	11.0 (10.0-13.0)	13.0 (10.0-17.0)	10.5 (8.0-12.0)	13.0 (12.0-19.8)
	p=0.925		p=0.106		p=0.218		p=0.005	
28-day mortality								
No. of death	1 (1.9%)	4 (8.0%)	0 (0%)	3 (21.4%)	1 (3.0%)	2 (7.4%)	0 (0%)	2 (11.1%)
Δ (pCKD-314-psoc) [95%CI]	-6.1% (-17.0%; 3.4% [p=0.155])		-21.4% (-47.6%; -1.1% [p=0.023])		-4.4% (-20.5%; 9.0% [p=0.439])		-11.1% (-32.8%; 8.2% [p=0.146])	
CRP								
Baseline (mean±SD)	80.0±64.9	74.9±57.2	76.1±72.1	74.8±49.3	94.0±69.9	82.1±54.2	105.2±82.2	78.6±54.1
CRP at day 11 (Change from baseline), mean±SD	20.5±29.6 (-59.5±73.7)	18.7±35.7 (-56.2±67.8)	28.9±40.1 (-47.3±88.7)	31.8±52.5 (-43.0±67.8)	17.0±26.1 (-76.9±75.1)	27.2±44.1 (-54.9±71.8)	14.4±19.4 (-90.8±88.5)	30.8±50.7 (-47.7±73.4)
	p=0.818		p=0.870		p=0.252		p=0.121	

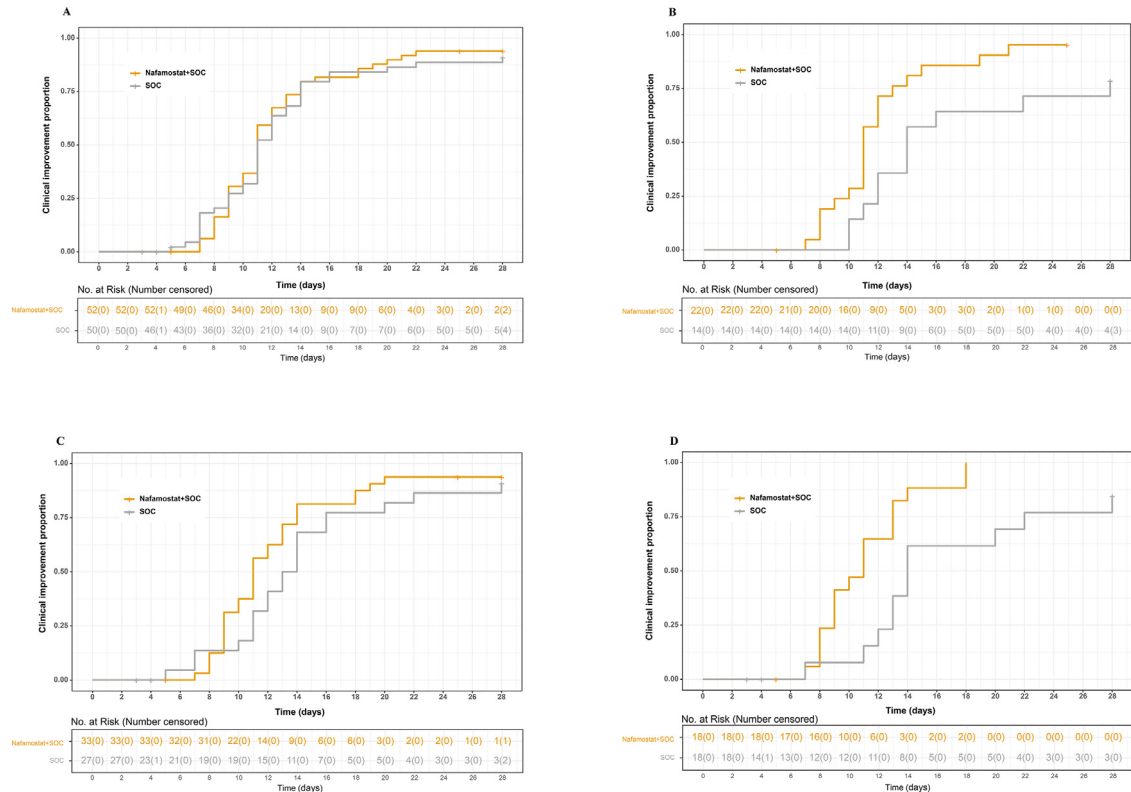


Fig. 2. Achievement of clinical improvement following nafamostat or Standard of Care (SOC). Kaplan–Meier Estimates are shown in the overall FAS population (A), in population aged over 65 years (B), in patients with NEWS ≥6 (C) and in patients with NEWS ≥7 (D). Deaths before day 28 were considered to be right censored at day 28. NEWS, National Early Warning Score; N, number of patients

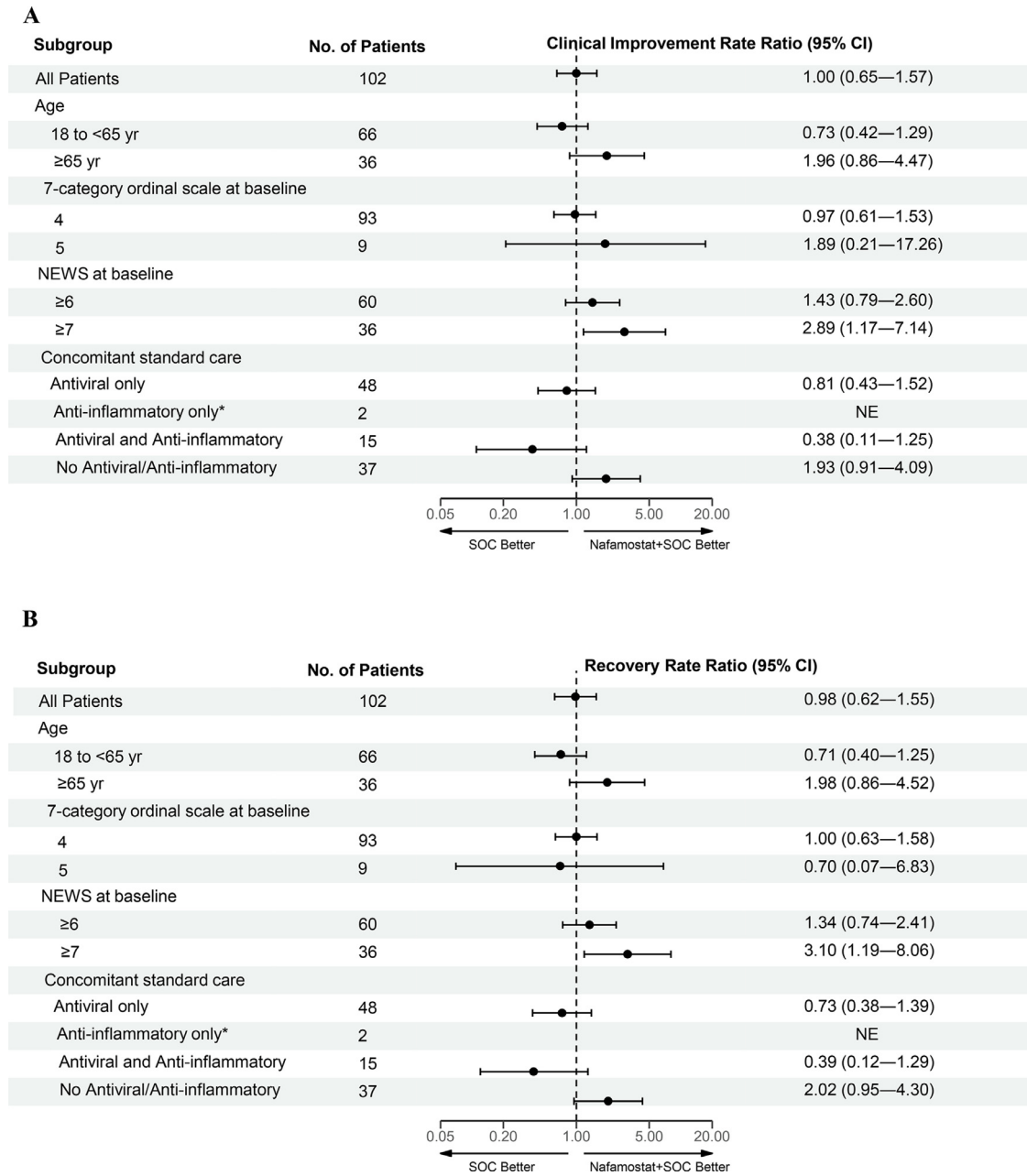


Fig. 3. Time to clinical improvement (A) and recovery (B) according to subgroup.

Forest plots are shown in time to clinical improvement (A) and time to recovery (B) according to subgroup: age, 7-category ordinal scale, NEWS at baseline and concomitant standard care including antiviral and anti-inflammatory agents which were considered according to treatment guidelines.

7-category ordinal scale 4 (hospitalization, requiring supplemental oxygen); 5 (hospitalization, requiring nasal high-flow oxygen therapy and/or noninvasive mechanical ventilation)

*NE denotes not possible to estimate.

CI, Confidential Interval; NEWS, National Early Warning Score; SOC, Standard of care

medicines have been used for a patient’s treatment. However, only enoxaparin showed an imbalance between the nafamostat and SOC groups in the safety population. Also, it should be noted that corticosteroid therapy was prohibited at randomisation and throughout the study, but it is now considered a key component of SOC for many patients who require oxygen. Since it was an open label clinical trial some bias could occur in relation to subjective endpoint assessments (e.g., hospital discharge and safety assessments). Taking this into account, endpoints such as NEWS scores are likely to be more reliable for the overall evaluation of the study. There is a possibility that an age imbalance between the two groups might affect the results, but

this was not the case for patients with NEWS ≥7 since the effects of nafamostat were clear and there was no age difference. Finally, for an accurate conclusion, the effect of NEWS ≥7 should be analyzed by age group, but there was a limit to such an analysis due to the small number of samples. Further study is needed in a larger phase 3 clinical trial.

In conclusion, in patients with a baseline NEWS ≥7 and not receiving corticosteroid therapy, nafamostat added to SOC was superior to SOC alone in accelerating clinical improvement and recovery in patients. Nafamostat was generally safe and had good tolerability with few serious AEs. Given these observed effects with nafamostat

Table 3
Summary of adverse events in the safety population.

Event	Nafamostat (N = 52)		SOC (N = 51)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any adverse event	25 (48.1)	5 (9.6)	16 (31.4)	8 (15.7)
Catheter site phlebitis	7 (13.5)	0 (0.0)	2 (3.9)	0 (0.0)
Hyponatraemia	4 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory failure	3 (5.8)	1 (1.9)	1 (2.0)	1 (2.0)
Abdominal pain	3 (5.8)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	2 (3.8)	0 (0.0)	1 (2.0)	0 (0.0)
Procedural pneumothorax	2 (3.8)	1 (1.9)	0 (0.0)	0 (0.0)
Blood pressure increased	1 (1.9)	1 (1.9)	2 (3.9)	0 (0.0)
Hyperthermia	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)
Blood pressure fluctuation	1 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)
Diarrhoea	1 (1.9)	0 (0.0)	1 (2.0)	0 (0.0)
Chest pain	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Infusion related reaction	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	1 (1.9)	0 (0.0)	1 (2.0)	0 (0.0)
Blood bilirubin increased	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram QT prolonged	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Glucose tolerance impaired	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperglycaemia	1 (1.9)	0 (0.0)	1 (2.0)	1 (2.0)
Hypoglycaemia	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphostasis	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnoea	0 (0.0)	0 (0.0)	3 (5.9)	2 (3.9)
Pulmonary embolism	0 (0.0)	0 (0.0)	2 (3.9)	2 (3.9)
Cardiac arrest	0 (0.0)	0 (0.0)	1 (2.0)	1 (2.0)
Serious adverse event	1 (1.9)		4 (7.8)	
Respiratory failure	1 (1.9) [†]		1 (2.0) [*]	
Procedural pneumothorax	1 (1.9) [†]		0 (0.0)	
Multiple organ failure	1 (1.9) ^{**}		0 (0.0)	
Pulmonary embolism	0 (0.0)		2 (3.9) [*]	
Cardiac arrest	0 (0.0)		1 (2.0) [*]	

*Serious AE leading to death

[†]Serious AEs reported in the same patient

Note. Not presented all AEs recorded in the SOC group and the grade 1 or 2 AEs but recorded in the SOC group only excluded from the table.

in hospitalised patients with NEWS ≥ 7 , a further phase 3 clinical trial is required to evaluate the efficacy of nafamostat for the treatment of COVID-19.

Author Contributions

SVZ was the coordinating investigator and OKK, OOB, AIG and BMG were principal investigators of the study. SVZ, OKK, OOB, AIG and BMG contributed to the implementation of the study and interpretation of the data. SVZ contributed revising the manuscript for important intellectual content and had final responsibility for the decision to submit for publication with agreement of all authors. SK and KYH were involved in the study design, analysis and interpretation of the data, and contributed to writing the manuscript. All authors reviewed and approved the final manuscript.

Declaration of Competing Interest

SK and KYH are both employees of CKD Pharm. The Investigators declare that the research was supported by a grant from CKD Pharm, South Korea, and have no other relationships that could be construed as a potential conflict of interest.

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Data sharing statement

The datasets generated for this study and relevant documents including clinical study documents (e.g., study report, study protocol, statistical analysis plan) will be made available to be shared after publication of the manuscript in a peer-reviewed journal and if regulatory activities are complete, on requests directed to the corresponding author.

Prior to providing data, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

All such requests will be governed by Data Sharing Agreement. Upon approval and governed by an agreement, data are shared by CKD.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.eclinm.2021.101169](https://doi.org/10.1016/j.eclinm.2021.101169).

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