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Remdesivir in Adults with Severe COVID-19: Results of a Randomized, Double-blind, Placebo-controlled, Multicenter Trial

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Abstract:	Background No specific antiviral has been proven effective for treatment of severe COVID-19. Remdesivir (GS-5734), a nucleoside analogue prodrug, has inhibitory effects on pathogenic animal and human coronaviruses, including SARS-CoV-2 in vitro, and inhibits MERS-CoV and SARS-CoV replication and disease in animal models. Methods: We conducted a randomized, double-blind, placebo-controlled, multicentre trial. Adults hospitalized with laboratory confirmed SARS-CoV-2 infection, and interval from illness onset to enrollment of ≤12 days, SaO 2 ≤94% on room air or a PaO 2 /FiO 2 ratio less than 300mmHg, and radiologically confirmed pneumonia were randomly assigned in a 2:1 ratio to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2-9 in single daily infusions), or placebo for 10 days. Subjects were permitted the use of lopinavir-ritonavir. The primary endpoint was time to clinical improvement (censored at Day 28), defined as the time (in days) from randomization to study treatment (remdesivir or placebo) until a decline of two categories on a six-category ordinal scale of clinical status (1 discharged; 6 death) or discharged alive from hospital, whichever came first. This trial is registered with ClinicalTrials.gov, number NCT04257656. Findings: 237 patients with laboratory-confirmed COVID-19 underwent randomization (158 remdesivir; 79 control); one patient in the control group withdrew before receiving any study treatment. Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1.23, 95% CI 0.87-1.75), mortality at 28 days (13.9% vs 12.8%, difference 1.1; 95% CI, -8.1, 10.3), or in time to SARS-CoV-2 PCR negativity. Adverse events were reported in 65.2% of remdesivir recipients versus 64.1% in placebo recipients. Remdesvir was stopped early in 18 (11.6%) patients because of adverse effects, compared to 4 (5.1%) in the control group. Interpretation: In this study of hospitalized adult patients with severe COVID-19 that was terminated prematurely, remdesivir was not associated with clinical or virological benefits.

Title: Remdesivir in Adults with Severe COVID-19: Results of a Randomized, Double-blind, Placebo-controlled, Multicenter Trial

Running title: A Trial of Remdesivir in Adults with Severe COVID-19

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Research in context

Evidence before this study

We searched PubMed database, up to April 10, 2020, for published clinical trials evaluating the effect of remdesivir among patients with laboratory confirmed coronavirus disease 2019 (COVID-19). The search terms used were ("COVID-19" OR "2019-nCoV" or "SARS-CoV-2") AND "remdesivir" AND ("clinical trial" or "randomized controlled trial"). We identified no published clinical trials of the effect of remdesivir in patients with COVID-19.

Added value of this study

Our study is the first randomized, double-blind, placebo-controlled clinical trial evaluating the effect of intravenous remdesivir in adults hospitalized with severe COVID-19. The study was terminated before attaining the pre-specified sample size and was underpowered for an efficacy evaluation. In the intention-to-treat population, the primary endpoint of time to clinical improvement was numerically shorter in the remdesivir group compared to the control group (median 21.0 days vs. 23 days), but was not statistically significant different (hazard ratio 1.23; 95% CI 0.87 to 1.75). For other secondary endpoints, including 28-day mortality, duration of invasive mechanical ventilation, and time to SARS-CoV-2 PCR negativity, no statistically significant differences were observed.

Implications of all the available evidence

No significant benefits were observed for remdesvir treatment beyond standard of care. Our trial did not attain the predetermined sample size because the outbreak of COVID-19 was brought under control in China. Future studies of remdesivir, including earlier treatment in COVID-19 patients and higher dose regimens or in combination with other antivirals or SARS-CoV-2

neutralizing antibodies in those with severe COVID-19 are needed to better understand its potential effectiveness.

ABSTRACT

Background No specific antiviral has been proven effective for treatment of severe COVID-19. Remdesivir (GS-5734), a nucleoside analogue prodrug, has inhibitory effects on pathogenic animal and human coronaviruses, including SARS-CoV-2 in vitro, and inhibits MERS-CoV and SARS-CoV replication and disease in animal models.

Methods: We conducted a randomized, double-blind, placebo-controlled, multicentre trial. Adults hospitalized with laboratory confirmed SARS-CoV-2 infection, and interval from illness onset to enrollment of ≤12 days, SaO_2 ≤94% on room air or a PaO_2/FiO_2 ratio less than 300mmHg, and radiologically confirmed pneumonia were randomly assigned in a 2:1 ratio to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2-9 in single daily infusions), or placebo for 10 days. Subjects were permitted the use of lopinavir-ritonavir. The primary endpoint was time to clinical improvement (censored at Day 28), defined as the time (in days) from randomization to study treatment (remdesivir or placebo) until a decline of two categories on a six-category ordinal scale of clinical status (1 = discharged; 6 = death) or discharged alive from hospital, whichever came first. This trial is registered with ClinicalTrials.gov, number NCT04257656.

Findings: 237 patients with laboratory-confirmed COVID-19 underwent randomization (158 remdesivir; 79 control); one patient in the control group withdrew before receiving any study treatment. Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1.23, 95% CI 0.87-1.75), mortality at 28 days (13.9% vs 12.8%, difference 1.1; 95% CI, -8.1, 10.3), or in time to SARS-CoV-2 PCR negativity. Adverse events were reported in 65.2% of remdesivir recipients versus 64.1% in placebo recipients. Remdesvir was stopped early in 18 (11.6%) patients because of adverse effects, compared to 4 (5.1%) in the control group.

Interpretation: In this study of hospitalized adult patients with severe COVID-19 that was terminated prematurely, remdesivir was not associated with clinical or virological benefits.

Funding: Chinese Academy of Medical Sciences (CAMS) Emergency Project of COVID-19 (2020HY320001); National Key Research and Development Program of China (2018YFC1200102); The Beijing Science and Technology Project (Z19110700660000).

Keywords: COVID-19, Remdesivir, Clinical Trial, Severe Illness.

INTRODUCTION

The ongoing pandemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections has caused over 1,777,666 illnesses and 108,867 deaths globally as of 12 April 2020[1]. Although most infections are self-limited, approximately 15% of infected adults develop severe pneumonia that requires treatment with supplemental oxygen and an additional 5% progress to critical illness with hypoxemic respiratory failure, acute respiratory distress syndrome, and multi-organ failure that necessitates ventilatory support, often for several weeks [2–4]. One-half or more of patients with coronavirus infectious disease-2019 (COVID-19) patients requiring invasive mechanical ventilation have died in hospital [4,5], and the associated burden on healthcare systems, especially intensive care units, has been overwhelming in several affected countries.

Although several approved drugs and investigational agents have shown antiviral activity against SARS-CoV-2 in vitro [6,7], at present there are no antiviral therapies of proven value in treating severely ill COVID-19 patients. Small observational studies enrolling predominantly those with mild illness have reported possible clinical benefit of hydroxychoroquine (alone or combined with azithromycin)[8]. An RCT enrolling patients within 12 days of symptom onset found that favipiravir was superior to arbidol in the proportion of those with mild illness who had recovered clinically by day 7 (56% vs 71%), but not in those with critical illness (0 vs 6%) [9]. In severe illness, one uncontrolled study of five patients given convalescent plasma suggested possible benefit, although the patients already had detectable anti-SARS-CoV-2 neutralizing antibodies before receipt of the plasma [10]. An open-label RCT of oral lopinavir-ritonavir found no significant effect on the primary outcome measure of time to clinical improvement (median, 16 days) and no evidence of reduction in viral RNA titers compared to control [11]. However, per-protocol analyses suggested possible

reductions in time to clinical improvement (difference of 1 day), particularly in those treated within 12 days of symptom onset. Further studies of lopinavir-ritonavir and other agents are ongoing.

Remdesivir (also GS-5734) is monophosphoramidate prodrug of an adenosine analog that has a broad antiviral spectrum including filo-, paramyxo-, pneumo- and coronaviruses [12,13]. Remdesivir is inhibitory in vitro for all human and animal coronaviruses tested to date including SARS-CoV-2 [13–15] and has shown antiviral and clinical effects in animal models of SARS-CoV and Middle East Respiratory Syndrome (MERS)-CoV infections [13,16,17]. In a lethal murine model of MERS, remdesivir was superior to a regimen of combined interferon-beta and lopinavir-ritonavir [16]. Remdesivir is a potent inhibitor of SARS-CoV-2 replication in human nasal and bronchial airway epithelial cells [18]. Intravenous remdesivir was studied for treatment of Ebola virus disease, in which it was adequately tolerated but less effective than several monoclonal antibody therapeutics [19], and has been used through individual compassionate use basis in over the last several months in certain countries to date [20]. Case studies have suggested benefit in severely ill COVID-19 patients [5,20,21]. However, the clinical and antiviral efficacy of remdesivir remains to be established. Here we report the results of an RCT of remdesivir in severe COVID-19 illness.

METHODS

Trial design and oversight

This was an investigator-initiated, individually randomized, placebo-controlled, double-blind trial to evaluate the efficacy and safety of intravenous remdesivir planned in 453 adults (≤18 years) hospitalized with severe COVID-19 illness. The trial was conducted from 6 February to 1 April 2020 at nine hospitals in Wuhan, Hubei Province, People's Republic of China (see Supplementary Appendix). Eligible patients were randomized 2:1 to either intravenous remdesivir (200 mg on day

1 followed by 100 mg on days 2-9 in single daily infusions) or placebo infusions for a total of 10 days (both provided by Gilead Sciences, Foster City, California). Randomization was stratified according to the level of respiratory support: (1) no oxygen support or oxygen support with nasal duct or mask; (2) high-flow oxygen, non-invasive ventilation, invasive ventilation, or extra-corporeal membrane oxygenation (ECMO). The permuted block (30 patients per block) randomization sequence, including stratification, was prepared by a statistician not involved in the trial using SAS software, version 9.4 (SAS Institute). Eligible patients were allocated to receive medication in individually numbered packs, according to the sequential order of the randomization centre (Jin Yin-Tan Hospital central pharmacy). Envelopes were prepared for emergency unbinding.

The trial was approved by the institutional review boards of each participating hospital. Written informed consent was obtained from all patients, or their legal representative if they were too unwell to provide consent. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization–Good Clinical Practice guidelines.

Patients

Males and non-pregnant female patients aged ≥18 years were eligible if they were RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had a SaO_2 ≤94% on room air or a PaO_2/FiO_2 ratio ≤300mgHg, and were within 12 days of illness onset. Eligible subjects of child-bearing age (male or female) agreed to take effective contraceptive measures (including hormonal contraception, barrier methods or abstinence) during the study period and for at least 7 days following the last study drug administration. Exclusion criteria included pregnancy

or breast-feeding; hepatic cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the ULN; known severe renal impairment (estimated eGFR< 30 mL/min/1.73m^2), or having received continuous renal replacement therapy (CRRT), hemodialysis or peritoneal dialysis; possibility of transfer to a non-study hospital within 72h; and enrollment into an investigational treatment study for COVID-19 within 30 days prior to screening. The use of other treatments, including lopinavir-ritonavir, was permitted.

Clinical and laboratory monitoring

Patients were assessed once daily by trained nurses using diary cards that captured data on a 6-category ordinal scale and safety from day 0 to day 28, hospital discharge, or death. Other clinical data was recorded using the World Health organization (WHO) - International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) case record form [22]. The safety evaluation included daily monitoring for adverse events (AEs), clinical laboratory testing (days 1, 3, 7 and 10), 12-lead electrocardiogram (ECG)(days 1, 14), and daily vital signs measurements (see Protocol for details[23]). Clinical data were recorded on paper case record forms and then double entered into an electronic database and validated by trial staff. Nasopharyngeal or oropharyngeal swabs, lower respiratory tract samples (sputum/tracheal aspiration/alveolar lavage fluid) as available, and fecal/anal swab specimens were collected on days 1, 3, 5, 7, 10, 14, 21, and 28 for viral RNA detection and quantification.

The trial was monitored by a contract research organization (Hangzhou Tigermed Consulting Co., Ltd[24]). Virologic testing was done at Teddy Clinical Research Laboratory (Tigermed- DiAn Joint Venture) using quantitative real-time RT-PCR. RNA was extracted from clinical samples with the MagNA Pure 96 system, detected and quantified by Cobas z480 qPCR (Roche, switzerland), using LightMix Modular SARS-CoV-2 assays (TIB MOBIOL, Berlin, Germany). Baseline the upper

(nasopharyngeal, NP or Oropharyngeal swabs, OP) and lower respiratory tract specimens were tested for detection of E gene, RdRp gene and N gene, then samples on the subsequent visits were quantitatively and qualitative detected for E gene.

Outcome measures

The primary clinical endpoint was time to clinical improvement (TTCI) within 28 days after randomization. Clinical improvement was defined as a 2-point reduction in subjects' admission status on a 6-point ordinal scale, or live discharge from the hospital, whichever came first. The 6 point scale included death: 6; hospitalized for ECMO and/or mechanical ventilation: 5; hospitalized for noninvasive ventilation and/or high flow oxygen therapy: 4; hospitalized for oxygen therapy (but not requiring high flow or noninvasive ventilation): 3; hospitalization but not requiring oxygen therapy: 2; discharged or having reached discharge criteria (defined as clinical recovery, i.e., normalization of pyrexia, respiratory rate [< 24/minute], and SpO2 [>94% on room air], and relief of cough, all maintained for at least 72 hours): 1. The 6-point scale was modified from the 7-point scale used in our previous COVID-19 lopinavir-ritonavir treatment[11] by collapsing the two outpatient strata into one.

Secondary outcomes included the proportions of subjects in each category of the 6-point scale within 7, 14, and 28 days of randomization; all-cause mortality within 28 days; frequency of invasive mechanical ventilation; duration of oxygen therapy; duration of hospitalization; and incidence of nosocomial infection (see Supplementary Appendix). Virologic measures included the proportions with viral RNA detection over time and viral RNA titer area-under-the-curve (AUC) measurements. Safety outcomes included treatment-emergent adverse events (AEs), serious AEs, and premature discontinuations of study drug.

Statistical Analysis

The original design required a total of 325 events across both arms, since this would provide 80% power under a one-sided type I error of 2.5% if the hazard ratio comparing remdesivir to placebo is 1.4 which corresponds to a change in TTCI to 15 days assuming that TTCI is 21 days on placebo. One interim analysis using triangular boundaries[25] and a 2:1 allocation ratio between remdesivir and placebo has been accounted for in the original design. Assuming an 80% event rate within 28 days across both arms and a drop-out rate of 10% implies that approximately 453 patients were to be recruited for this trial (151 on placebo and 302 on remdesivir). The possibility for an interim analysis after enrollment of approximately 240 subjects was included in the design if requested by the independent data safety and monitoring board (DSMB). However, no subjects were enrolled after 12 March 2020 due to the control of the outbreak in Wuhan, and on 29 March the DSMB recommended that the study be terminated and analyzed. When all the other assumptions stayed the same, with the actual enrolment of 236 participants, the statistical power reduced from 80% to 58%.

The primary efficacy analysis was on an intention-to-treat (ITT) basis with all randomized patients. TTCI was assessed after all patients had reached Day 28; failure to reach clinical improvement or death before Day 28 were considered as right-censored at day 28. TTCI was portrayed by Kaplan-Meier plot and compared with a log-rank test. The hazard ratio (HR) 95% confidence intervals (CI) for clinical improvement and hazard ratio with 95% CI for clinical deterioration was calculated by Cox proportional-hazards model. Other analyses include subgroup analyses for those randomized ≤10 or >10 days after illness onset, time-to-clinical deterioration (defined as one category increase or death), and for viral RNA load at entry. We present adverse event data on the patients' actual treatment exposure, coded using Medical Dictionary for Regulatory Activities

(MedDRA). Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc.).

This trial is registered with ClinicalTrials.gov, number NCT04257656.

RESULTS

Patients

Among 255 patients who were screened, 237 patients were eligible, consented and were randomized, of whom 1 withdrew. 158 were assigned to receive remdesivir and 78 to receive placebo. In the remdesivir group, 155 (98.1%) received remdesivir as assigned and placebo was given to all patients in the control group (Figure 1). The median age of study patients was 65 years (interquartile range [IQR], 56 to 71 years) and 140 (59.3%) were males. The most common comorbidity was hypertension (43.2%), followed by diabetes (23.7%) and coronary heart disease (7.2%). Lopinavir-ritonavir was co-administered in 42 (17.8%) patients at day 1 (Table 1). Most patients (81.6% in the remdesivir and 83.3% in the control group) were in category 3 of the six-point ordinal scale of clinical status at baseline. There were more patients (60.3%) in the control group than in the remdesivir group (44.3%) who had been symptomatic for 10 days or less at the time of randomization. No other major differences in symptoms, signs, laboratory results, disease severity, or treatments were observed between groups at baseline.

The median days from illness onset to randomization was 10 days (IQR 9 to 12 days). No important differences were apparent between the groups in other treatments received (including lopinavir-ritonavir or corticosteroids) (Table 2). During the whole period of hospitalization, 155 (65.7%) patients received corticosteroids, with the median time from illness onset to corticosteroids therapy

being 8.5 days (IQR, 6.5 to 11.0 days), while 91 (38.6%) patients received corticosteroids before enrollment.

Primary outcome

In the intention-to-treat population, the time to clinical improvement in the remdesivir group was non-significantly shorter than the control group (median 21.0 days vs. 23 days; hazard ratio 1.23; 95% CI 0.87 to 1.75) (Table 3 and Figure 2). Results for TTCI were similar in the per-protocol population (median 21.0 days vs, 23.0 days, respectively hazard ratio 1.27; 95% CI 0.89 to 1.80) (Table S1 and Figure S1). Although not statistically significant, remdesivir was associated with a faster time to clinical improvement as compared to placebo among patients with symptom duration of 10 days or less in the intention-to-treat population (Figure S2). If clinical improvement was defined as a one, instead of two, category decline, the hazard ratio was 1.34 with 95% CI of 0.96 to 1.86 (Figure S3). Time-to-clinical deterioration, defined as a one category increase or death, the hazard ratio was 0.95 with 95% CI of 0.55 to 1.64 (Figure S4).

Secondary outcome

The 28-day mortality was similar between the two groups (13.9% in remdesivir vs. 12.8% in placebo; difference 1.1; 95% CI -8.1 to 10.3). Use of remdesivir within 10 days after symptom onset was associated with a non-significantly lower 28-day mortality (5.1% vs. 9.0%; difference -3.9; 95% CI -11.1 to 3.3), while late use was non-significantly associated with a higher 28-day mortality (7.6% vs. 3.8%; difference 3.7; 95% CI -2.2 to 9.7). The clinical improvement rates at days 14 and day 28 were higher in remdesivir group but this was non-significant (26.6% vs. 23.1% at day 14; 65.2% vs. 57.7% at day 28). For patients assigned to remdesivir group, the invasive mechanical ventilation (IMV) duration was numerically shorter than those assigned to control

group (median 7.0 days vs. 15.5 days; difference 4.0 days; 95% CI -2.0 to 14.0 days) but the number of patients was small. No significant differences were observed between the two groups in length of oxygen support, hospital length of stay, days from randomization to discharge, days from randomization to death and distribution of six-category scale at day 7, day 14 and day 28. (Table 3 and Figure S5)

Virology

Of 236 patients who were RT-PCR positive at enrollment, 37 (15.7%) had undetectable viral RNA on the NP/OP swab taken after consent. The mean baseline viral load of NP/OP swabs was 4.7 ± 2.8 log10 copies/mL in the remdesivir group and 4.7 ± 2.4 log10 copies/mL in the control group (Table 1). The viral load decreased over time equally in both groups (Figure 3A). No difference in viral load were observed when stratified by interval from illness onset to randomization (Figure S6 A&B). The findings of viral load reduction were similar by lower respiratory specimens (Figure 3B)

The cumulative rate of undetectable viral RNA of NP/OP swabs by day 28 was 64.8%, and the proportion negative was similar among patients receiving remdesivir and those receiving placebo (day 3, 23.4% to 24.4%; day 5, 33.5% to 32.1%; day 7, 41.8% to 41.0%; day 10, 51.9% to 57.7%; day 14, 58.9% to 62.8%; day 21, 62.0% to 67.9%; day 28, 62.7% to 69.2%) (Table S2).

Safety

Adverse events were reported in 102 (65.8%) patients in the remdesivir group and 50 (64.1%) in the control group. The most common adverse events in the remdesivir group were constipation (13.5%), hypoalbuminemia (12.9%), hypokalemia (11.6%), anaemia (11.6%), thrombocytopenia (10.3%), and increased total bilirubin (9.7%), and in control group were hypoalbuminemia (15.4%),

constipation (15.4%), anaemia (15.4%), hypokalemia (14.1%), increased aspartate aminotransferase (11.5%), elevated blood lipids (10.3%), and increased total bilirubin (9.0%). A total of 28 (18.1%) serious adverse events were reported in the remdesivir group and 20 (25.6%) in the control group. More patients in the remdesivir group discontinued drug for adverse events or serious adverse events (11.6% vs. 5.1%), among whom 7 (4.5%) were due to respiratory failure or ARDS in remdesivir group. All deaths during the observation period were judged by the site investigators to be unrelated to the intervention. (Table 4)

DISCUSSION

Our trial found that intravenous remdesivir did not significantly improve the time to clinical improvement (TTCI), mortality, or time to clearance of virus in patients with serious COVID-19 illness compared to placebo. Compared to a recent study of compassionate use remdesivir that suggested clinical benefit[20], our study population was not as ill (at time of enrollment 0.4% on invasive mechanical ventilation or ECMO versus 64%) and was treated somewhat earlier in their disease course (median, 10 days versus 12 days). Such differences might be expected to favor remdesivir providing greater effects in our study population, but we did not find this. However, our study did not reach its target enrollment because the stringent public health measures employed in Wuhan City led to marked reductions in new patient presentations in mid-March, and restrictions on hospital bed availability resulted in most patients being enrolled later in the course of disease. Consequently, we could not adequately assess whether earlier remdesivir treatment might have provided clinical benefit. In one murine model of SARS, remdesivir treatment starting at 2 days post infection, after virus replication and lung airway epithelial damage had already peaked, significantly reduced SARS-CoV lung titers but did not decrease disease severity or

mortality [13]. A need for early treatment has been found in nonhuman primate models of SARS and MERS in which virus replication is very short-lived and lung pathology appears to develop more rapidly than in human infections[13,16,17]. Such findings argue for testing of remdesivir earlier in COVID-19 illness.

Remdesivir did not result in significant reductions in SARS-CoV-2 RNA loads or detectability in upper respiratory tract or sputum specimens in this study despite showing strong antiviral effects in pre-clinical models of CoV infection. In African green monkey kidney Vero E6 cells remdesivir inhibited SARS-CoV-2 with a 50% effective concentration (EC_{50}) of 0.46 ug/ml and EC_{90} of 1.06 ug/ml [6]. In human nasal and bronchial airway epithelial (HAE) cells, a fixed 20 uM (12.1 ug/ml) concentration reduced estimated intracellular viral titers over 7.0 at 48 hours [18]. In human airway epithelial cells, remdesivir's EC_{50} was 0.042 ug/ml for SARS-CoV and 0.045 ug/ml for MERS-CoV [13]. In a murine model of MERS subcutaneous remdesivir demonstrated significant antiviral and clinical effects with a dose regimen that maintained plasma concentrations above 1 uM (0.60 ug/ml) throughout the dosing interval [13]. In rhesus macaques a 5 mg/kg dose, reported to be roughly equivalent to 100-mg daily dosing in humans, was effective for treatment of MERS-CoV infection and reduced pulmonary virus replication when started at 12 hours post infection [18]. Healthy adult volunteers receiving a doses similar to our trial (200-mg on day, 100-mg on days 2-4) had mean peak plasma concentrations of 5.4 ug/ml on day 1and 2.6 ug/ml on day 5. [26]. Doses of 150 mg/day for 14 days have been adequately tolerated in healthy adults, and a daily dose regimen of 150 mg for 3 days followed by 225 mg for 11 days appeared to be generally well-tolerated in one patient with Ebola meningo-encephalitis [27]. However, the pharmacokinetics of remdesivir in severely ill patients, and particularly the concentrations of the active nucleotide metabolite (GS-441524)

triphosphate in respiratory tract cells of treated patients, are unknown. Studies of higher dose regimens for which there are safety data (eg, 200 mg daily doses) warrant consideration.

Our study found that remdesivir was adequately tolerated and no new safety concerns were identified. The overall proportion of patients with serious adverse events tended to be lower in remdesivir recipients compared to placebo (Table 3). However, a higher proportion of remdesivir recipients had dosing prematurely stopped by the investigators for adverse events (11.6% versus 5.1% placebo) for various reasons including gastrointestinal symptoms (anorexia, nausea, vomiting), transaminase or bilirubin elevations, and worsened cardiopulmonary status.

In addition to its diminished power to detect differences in clinical outcomes and initiation of treatment relatively late in COVID-19, our trial provided limited data on lower respiratory tract virus detection and lacked data on infectious virus recovery or on possible emergence of reduced susceptibility to remdesivir. Coronaviruses partially resistant to inhibition by remdesivir (~6-fold increased EC_{50}) have been obtained following serial in vitro passage, but these viruses remain susceptible to higher remdesivir concentrations and show impaired fitness [28]. Another limitation of the trial was the high frequency of systemic corticosteroid use, which could have contributed to prolongation of viral replication, as observed in SARS [29] and MERS [30] and possibly diminished the likelihood of observing an antiviral effect with remdesivir.

In summary we found that this dose regimen of intravenous remdesivir was adequately tolerated but did not provide significant clinical or antiviral effects in seriously ill COVID-19 patients. Future studies with larger sample sizes will continue to inform on remdesivir's effect on COVID-19. Furthermore, strategies to enhance remdesivir's antiviral potency (e.g., higher dose regimens, combination with other antivirals or SARS-CoV-2 neutralizing antibodies) and to mitigate

immunopathologic host responses contributing to COVID-19 severity (e.g., inhibitors of IL-6, IL-1, TNF-a) require rigorous study.

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Conflicts of interest

The authors have no conflict of interest or financial relationships to disclose. FGH has served as non-compensated consultant to Gilead Sciences on its respiratory antiviral program. No form of payment was given to anyone to produce the manuscript. All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Author Contributions:

Dr. Bin Cao, Dr. Chen Wang and Dr. Yeming Wang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Chen Wang and Dr. Bin Cao decided to publish the paper.

Study concept and design: Bin Cao, Chen Wang, Yeming Wang, Peter W. Horby, Thomas Jaki and Frederick G. Hayden provide input on the trial design.

All authors contributed to the trial conduct.

Acquisition, analysis, and interpretation of data: Bin Cao, Chen Wang, Yeming Wang, Frederick Hayden and Peter Horby

Drafting of the manuscript: Yeming Wang, Frederick Hayden, Peter Horby, Guohui Fan.

Critical revision of the manuscript: Bin Cao, Chen Wang, Peter Horby, Frederick Hayden, Guohui Fan, Thomas Jaki, and Xiaoying Gu.

Statistical analysis: Yeming Wang and a statistician (Joe Yao) from Tigermed Consulting Co., Ltd. Guohui Fan gave valuable suggestions for data analysis.

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Table

Table 1. Baseline Demographic and Clinical Characteristics of the Patients

Characteristics	Total (n = 236)	Remdesivir group (n = 158)	Control group (n = 78)
Age, yr	65.0 (56.0-71.0)	66.0 (57.0-73.0)	64.0 (53.0-70.0)
Gender, male, n (%)	140 (59.3)	89 (56.3)	51 (65.4)
Any co-morbidities	167 (70.8)	112 (70.9)	55 (70.5)
Hypertension	102 (43.2)	72 (45.6)	30 (38.5)
Diabetes, n (%)	56 (23.7)	40 (25.3)	16 (20.5)
Coronary heart disease, n (%)	17 (7.2)	15 (9.5)	2 (2.6)
Body temperature, ℃	36.8 (36.5-37.2)	36.8 (36.5-37.2)	36.8 (36.5-37.2)
Fever, n (%)	87 (36.9)	56 (35.4)	31 (39.7)
Respiratory rate > 24 /min, n (%)	47 (19.9)	36 (22.8)	11 (14.1)
White blood cell count (× 109/L)	6.3 (4.5-8.3)	6.2 (4.4-8.3)	6.4 (4.5-8.3)
4-10, n (%)	166 (70.3)	108 (68.4)	58 (74.4)
<4, n (%)	39 (16.5)	27 (17.1)	12 (15.4)
>10, n (%)	28 (11.9)	20 (12.7)	8 (10.3)
Lymphocyte count (× 109/L)	0.8 (0.6-1.1)	0.8 (0.6-1.1)	0.7 (0.6-1.2)
⩾ 1.0, n (%)	72 (30.5)	49 (31.0)	23 (29.5)
< 1.0, n (%)	161 (68.2)	106 (67.1)	55 (70.5)
Platelet count (× 109/L)	187.0 (143.0-251.0)	183.0 (144.0-235.0)	194.5 (141.0-266.0)
⩾ 100, n (%)	223 (94.5)	148 (93.7)	75 (96.2)
< 100, n (%)	10 (4.2)	7 (4.4)	3 (3.8)
Serum creatinine (μmol/L)	69.4 (56.0-84.3)	68.0 (56.0-82.0)	71.3 (56.0-88.7)
⩽ 133, n (%)	227 (96.2)	151 (95.6)	76 (97.4)
> 133, n (%)	5 (2.1)	3 (1.9)	2 (2.6)
Aspartate aminotransferase (U/L)	32.0 (23.0-46.0)	31.0 (22.0-44.0)	33.0 (24.0-48.0)
⩽ 40, n (%)	158 (66.9)	109 (69.0)	49 (62.8)
> 40, n (%)	75 (31.8)	46 (29.1)	29 (37.2)
Alanine aminotransferase (U/L)	26.0 (18.0-43.0)	26.0 (18.0-42.0)	26.0 (20.0-43.0)
⩽ 50	196 (83.1)	130 (82.3)	66 (84.6)
> 50	37 (15.7)	25 (15.8)	12 (15.4)
Lactate dehydrogenase (U/L)	334.0 (248.0-437.0)	339.0 (247.0-441.5)	329.0 (249.0-411.0)
⩽ 245	53 (22.5)	36 (22.8)	17 (21.8)
> 245	170 (72.0)	112 (70.9)	58 (74.4)
Creatine kinase (U/L)	75.5 (47.0-145.0)	75.9 (47.0-131.1)	75.0 (47.0-158.0)
⩽ 185	172 (72.9)	118 (74.7)	54 (69.2)
> 185	36 (15.3)	23 (14.6)	13 (16.7)

NEWS2 score at day 1	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	4.0 (3.0, 6.0)
Six-category scale at day 1			
2 Hospitalization, not requiring supplemental oxygen, n (%)	3 (1.3)	0	3 (3.8)
3 Hospitalization, requiring supplemental oxygen, n (%)	194 (82.2)	129 (81.6)	65 (83.3)
4 Hospitalization, requiring HFNC and/or non-IMV, n (%)	37 (15.7)	28 (17.7)	9 (11.5)
5 Hospitalization, requiring ECMO and/or IMV, n (%)	1 (0.4)	0	1 (1.3)
6 Death	1 (0.4)	1 (0.6)	0
Mean baseline viral load of NP/OP swabs (SD), log10 copies/mL	4.7 ±2.6	4.7 ±2.8	4.7±2.4
Receiving injection of interferon α2b at day 1, n (%)	44 (18.6)	29 (18.4)	15 (19.2)
Receiving lopinavir-ritonavir at day 1, n (%)	42 (17.8)	27 (17.1)	15 (19.2)
Antibiotic at baseline, n (%)	184 (78.0)	121 (76.6)	63 (80.8)
Corticosteroids therapy at baseline, n (%)	91 (38.6)	60 (38.0)	31 (39.7)

Note. Numbers in parenthesis correspond to interquartile range observed value for continuous variables and to percentages for indicator variables as appropriate.

Table 2. Any Treatments Received before and after Enrollment.

Characteristics	Total (n = 236)	Remdesivir group (n = 158)	Control group (n = 78)
Days from illness onset to starting drug (days)	10.0 (9.0, 12.0)	11.0 (9.0, 12.0)	10.0 (8.0, 11.0)
Early (⩽10 days of symptom onset), n (%)	117 (49.6)	70 (44.3)	47 (60.3)
Late (> 10 days of symptom onset), n (%)	111 (47.0)	83 (52.5)	28 (35.9)
Receiving injection of interferon α2b, n (%)	76 (32.2)	46 (29.1)	30 (38.5)
Receiving lopinavir-ritonavir, n (%)	67 (28.4)	44 (27.8)	23 (29.5)
Vasopressors, n (%)	38 (16.1)	25 (15.8)	13 (16.7)
Renal replacement therapy, n (%)	6 (2.5)	3 (1.9)	3 (3.8)
Highest oxygen therapy support			
Non-invasive mechanical ventilation, n (%)	17 (7.2)	14 (8.9)	3 (3.8)
Invasive mechanical ventilation, n (%)	21 (8.9)	11 (7.0)	10 (12.8)
IMV+ECMO, n (%)	2 (0.8)	2 (1.3)	0
Antibiotic, n (%)	215 (91.1)	142 (89.9)	73 (93.6)
Corticosteroids therapy, n (%)	155 (65.7)	102 (64.6)	53 (67.9)
Days from illness onset to corticosteroids therapy (days)	8.5 (6.5, 11.0)	9.0 (7.0, 11.0)	8.0 (6.0, 10.0)
Days of corticosteroids therapy (days)	10.0 (6.0, 15.0)	9.0 (5.0, 15.0)	10.0 (6.0, 16.0)

Note. Numbers in parenthesis correspond to interquartile range observed value for continuous variables and to percentages for indicator variables as appropriate. Abbreviation: NEWS2 = National Early Warning Score 2; HFNC = high-flow nasal cannula for oxygen therapy; IMV = invasive mechanical ventilation; ECMO = extracorporeal membrane oxygenation; SD = standard deviation.

Table 3. Outcomes in the intention-to-treat population.

Characteristics	Total (n = 236)	Remdesivir group (n = 158)	Control group (n = 78)	Difference §
TTCI	22.0 (13.5 to 28.0)	21.0 (13.0 to 28.0)	23.0 (15.0 to 28.0)	1.23 (0.87 to 1.75)†
Day 28 mortality, n (%)	32 (13.6)	22 (13.9)	10 (12.8)	1.1 (-8.1 to 10.3)
Early (⩽10 days of symptom onset)	15 (6.4)	8 (5.1)	7 (9.0)	-3.9 (-11.1 to 3.3)
Late (> 10 days of symptom onset)	15 (6.4)	12 (7.6)	3 (3.8)	3.7 (-2.2 to 9.7)
Clinical improvement rates				
Day 7, n (%)	6 (2.5)	4 (2.5)	2 (2.6)	-0.0 (-4.3 to 4.2)
Day 14, n (%)	60 (25.4)	42 (26.6)	18 (23.1)	3.5 (-8.1 to 15.1)
Day 28, n (%)	148 (62.7)	103 (65.2)	45 (57.7)	7.5 (-5.7 to 20.7)
IMV duration (days)	8.0 (5.0 to 19.0)	7.0 (4.0 to 16.0)	15.5 (6.0 to 21.0)	4.0 (-2.0 to 14.0)
IMV duration in survivors (days) &	30.5 (17.0 to 42.0)	19.0 (5.0 to 42.0)	42.0 (17.0 to 46.0)	-12.0 (-41.0 to 25.0)
IMV duration in non-survivors (days) &	7.0 (4.0 to 15.0)	7.0 (2.0 to 11.0)	8.0 (5.0 to 16.0)	2.5 (-3.0 to 11.0)
Length of oxygen support (days)	20.0 (12.0 to 31.0)	19.0 (11.0 to 31.0)	21.0 (14.0 to 30.5)	2.0 (-1.0 to 6.0)
Hospital length of stay (days)	25.0 (16.5 to 37.0)	25.0 (16.0 to 38.0)	24.5 (18.0 to 36.0)	0.0 (-4.0 to 4.0)
Days from randomization to discharge (days)	21.0 (13.0 to 31.0)	21.0 (12.0 to 31.0)	21.0 (13.5 to 28.5)	0.0 (-3.0 to 3.0)
Days from randomization to death (days)	11.0 (6.0 to 18.0)	9.5 (6.0 to 18.5)	11.0 (7.0 to 18.0)	1.0 (-5.0 to 7.0)
Six-category scale at day 7				**0.69 (0.41 to 1.17)***
1 Discharge (alive)	6 (2.5)	4 (2.5)	2 (2.6)	
2 Hospitalization, not requiring supplemental oxygen, n (%)	37 (15.7)	21 (13.3)	16 (20.5)	
3 Hospitalization, requiring supplemental oxygen, n (%)	130 (55.1)	87 (55.1)	43 (55.1)	
4 Hospitalization, requiring HFNC and/or non-IMV, n (%)	34 (14.4)	26 (16.5)	8 (10.3)	
5 Hospitalization, requiring ECMO and/or IMV, n (%)	10 (4.2)	6 (3.8)	4 (5.1)	
6 Death	14 (5.9)	10 (6.3)	4 (5.1)	
Six-category scale at day 14				**1.25 (0.76 to 2.04)***
1 Discharge (alive)	57 (24.2)	39 (24.7)	18 (23.1)	
2 Hospitalization, not requiring supplemental oxygen, n (%)	31 (13.1)	21 (13.3)	10 (12.8)	
3 Hospitalization, requiring supplemental oxygen, n (%)	89 (37.7)	61 (38.6)	28 (35.9)	
4 Hospitalization, requiring HFNC and/or non-IMV, n (%)	21 (8.9)	13 (8.2)	8 (10.3)	

5 Hospitalization, requiring ECMO and/or IMV, n (%)	11 (4.7)	4 (2.5)	7 (9.0)	
6 Death	22 (9.3)	15 (9.5)	7 (9.0)	
Six-category scale at day 28				**1.14 (0.66 to 1.95)***
1 Discharge (alive)	136 (57.6)	91 (57.6)	45 (57.7)	
2 Hospitalization, not requiring supplemental oxygen, n (%)	18 (7.6)	14 (8.9)	4 (5.1)	
3 Hospitalization, requiring supplemental oxygen, n (%)	31 (13.1)	18 (11.4)	13 (16.7)	
4 Hospitalization, requiring HFNC and/or non-IMV, n (%)	4 (1.7)	2 (1.3)	2 (2.6)	
5 Hospitalization, requiring ECMO and/or IMV, n (%)	5 (2.1)	2 (1.3)	3 (3.8)	
6 Death	32 (13.6)	22 (13.9)	10 (12.8)	

Note. Number (percentage) or median (interquartile range) is summarized as appropriate. Abbreviation: ICU = intensive care unit; HFNC = high-flow nasal oxygen therapy; IMV = intensive mechanical ventilation; ECMO = extracorporeal membrane oxygenation; TTCI = time to clinical improvement. Clinical improvement (the event) was defined as a decline of two categories on the modified seven-category ordinal scale of clinical status, or hospital discharge.

* Calculated by ordinal logistic regression model.

& In survivors, 3 patients were in each group; In non-survivors, 10 patients were in remdesivir group, 7 cases in control group.

§ Differences were expressed as rate differences or Hodges-Lehmann estimator and 95% confidence intervals.

† The hazard ratio was estimated by COX proportional risk model.

Table 4. Summary of adverse events in safety population that occurred in more than one participant

Events	Remdesivir group (n = 155)		Control group (n = 78)	
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Any adverse event (in ⩾2% of patients in any treatment group) *	102 (65.8)	13 (8.4)	50 (64.1)	11 (14.1)
Hypoalbuminemia	20 (12.9)	0	12 (15.4)	1 (1.3)
Hypokalemia	18 (11.6)	2 (1.3)	11 (14.1)	1 (1.3)
Increased blood glucose	11 (7.1)	0	6 (7.7)	0
Anaemia	18 (11.6)	1 (0.6)	12 (15.4)	2 (2.6)
Rash	11 (7.1)	0	2 (2.6)	0
Thrombocytopenia	16 (10.3)	4 (2.6)	5 (6.4)	3 (3.8)
Increased total bilirubin	15 (9.7)	1 (0.6)	7 (9.0)	0
Elevated blood lipids	10 (6.5)	0	8 (10.3)	0
Elevated WBC	11 (7.1)	0	6 (7.7)	0
Hyperlipemia	10 (6.5)	0	8 (10.3)	0
Increased BUN	10 (6.5)	0	5 (6.4)	0
Elevated neutrophil	10 (6.5)	0	4 (5.1)	0
Aspartate aminotransferase increased	7 (4.5)	0	9 (11.5)	0
Constipation	21 (13.5)	0	12 (15.4)	0
Nausea	8 (5.2)	0	2 (2.6)	0
Diarrhoea	5 (3.2)	0	2 (2.6)	0
Vomiting	4 (2.6)	0	2 (2.6)	0
Reduced serum sodium	4 (2.6)	0	2 (2.6)	0
Increased serum potassium	4 (2.6)	2 (1.3)	1 (1.3)	0
Any serious adverse event*	28 (18.1)	9 (5.8)	20 (25.6)	10 (12.8)
Respiratory failure or acute respiratory distress syndrome	16 (10.1)	4 (2.6)	6 (7.7)	4 (5.1)
Cardiopulmonary failure	8 (5.2)	0	7 (9.0)	1 (1.3)
Pulmonary embolism	1 (0.6)	1 (0.6)	1 (1.3)	1 (1.3)
Recurrence of COVID-19	1 (0.6)	0	0	0
Cardiac arrest	1 (0.6)	0	0	0
Acute coronary syndrome	0	0	1 (1.3)	1 (1.3)
Tachycardia	0	0	1 (1.3)	0

Septic shock	1 (0.6)	0	1 (1.3)	1 (1.3)
Lung abscess	0	0	1 (1.3)	1 (1.3)
Sepsis	0	0	1 (1.3)	1 (1.3)
Bronchitis	0	0	1 (1.3)	1 (1.3)
Thrombocytopenia	1 (0.6)	1 (0.6)	0	0
Increased D-dimer	0	0	1 (1.3)	1 (1.3)
Hemorrhage of lower digestive tract	1 (0.6)	1 (0.6)	0	0
Ileus	0	0	1 (1.3)	0
Deep vein thrombosis	1 (0.6)	1 (0.6)	1 (1.3)	1 (1.3)
Acute kidney injury	1 (0.6)	0	0	0
Diabetic keto-acidosis	0	0	1 (1.3)	1 (1.3)
Multiple organ dysfunction syndrome	1 (0.6)	0	2 (2.6)	0
Any AE/SAE leading to discontinued drug	18 (11.6)	3 (1.9)	4 (5.1)	1 (1.3)
Respiratory failure or acute respiratory distress syndrome	7 (4.5)	1 (0.6)	1 (1.3)	0
Cardiopulmonary failure	3 (1.9)	0	1 (1.3)	0
Nausea	1 (0.6)	0	0	0
Vomiting	1 (0.6)	0	0	0
Ileus	0	0	1 (1.3)	0
Elevated ALT	2 (1.3)	1 (0.6)	0	0
Rash	2 (1.3)	0	0	0
Poor appetite	1 (0.6)	0	0	0
Increased total bilirubin	1 (0.6)	0	0	0
Acute kidney injury	1 (0.6)	1 (0.6)	0	0
Seizure	0	0	1 (1.3)	0
Aggravated schizophrenia	0	0	1 (1.3)	1 (1.3)
Aggravated depression	0	0	1 (1.3)	1 (1.3)

Data are n (%) and include all events reported after antiviral treatment.

*Some patients had more than one adverse event.

§ Totally,36 patients discontinued the drug, 22 cases for AE/SAE, 14 patients for other reason (such as hospital discharge or early death). Detailed individual reasons for drug discontinuing was listed in appendix.

Figure 1. Trial profile

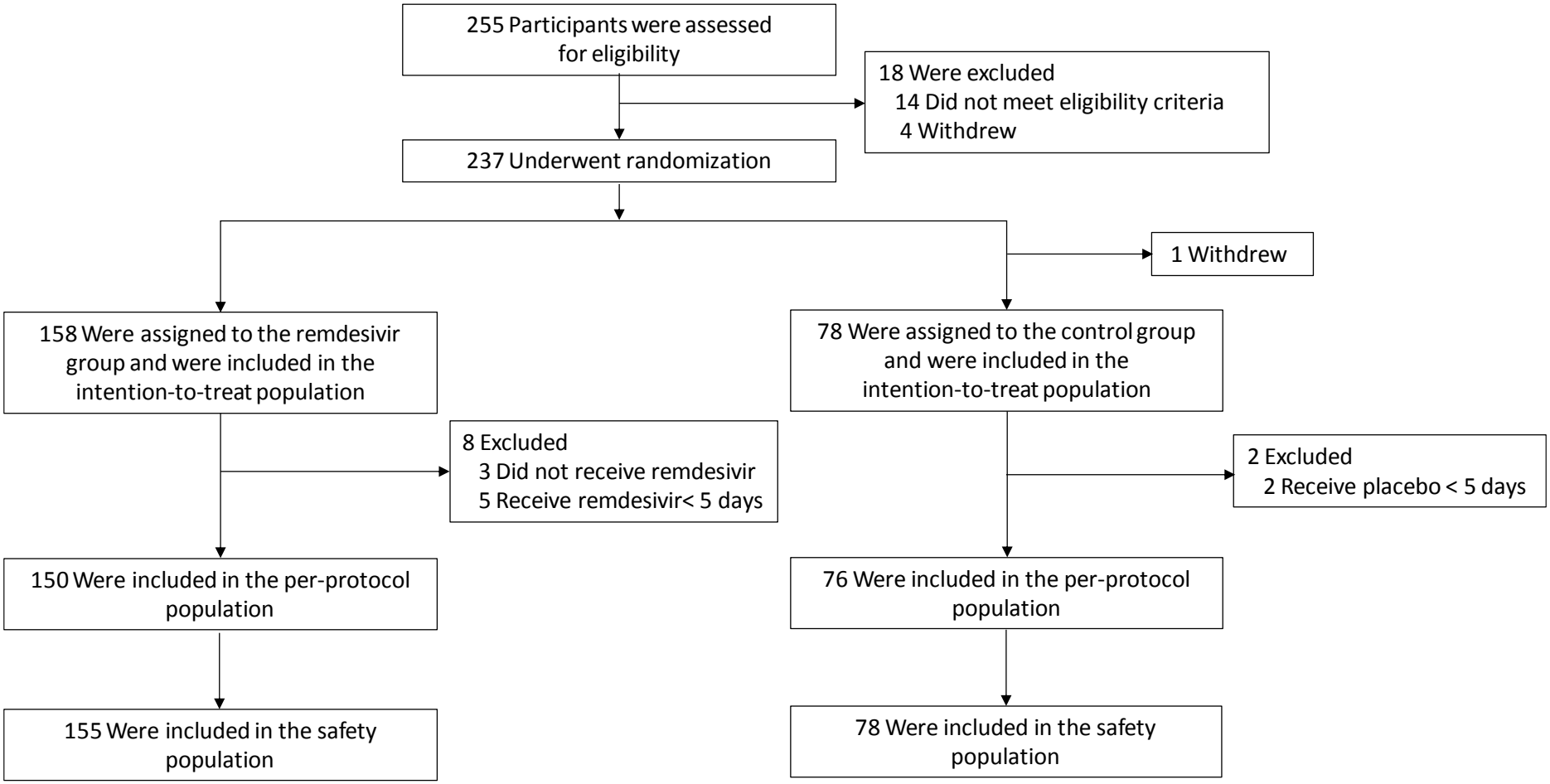
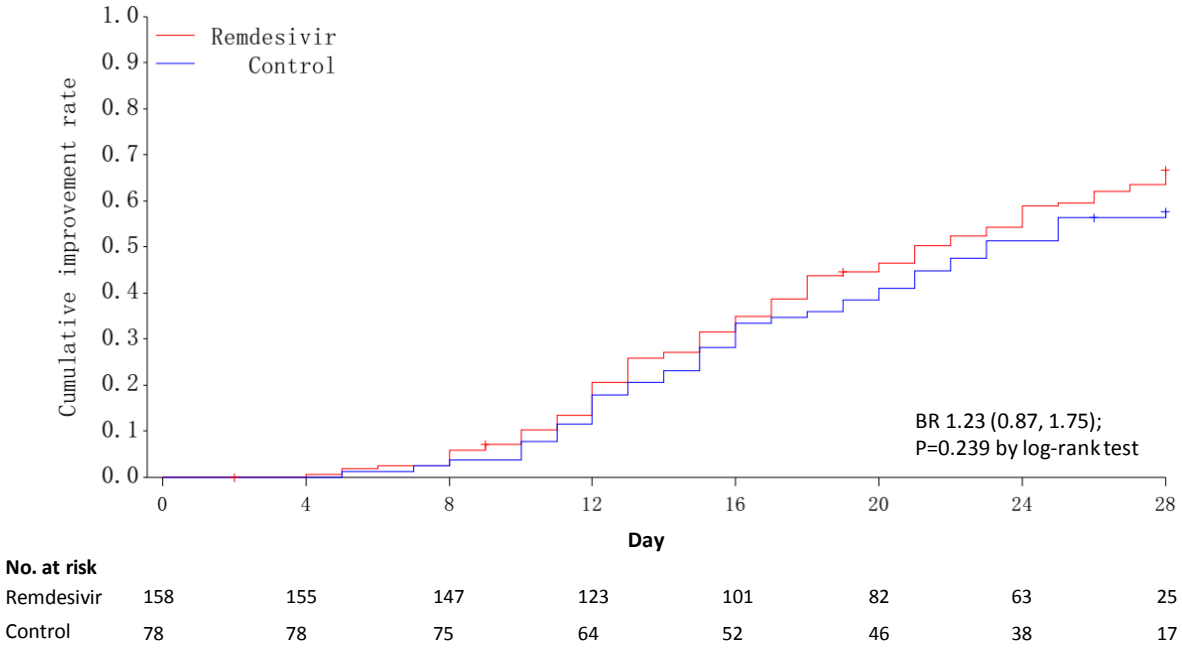


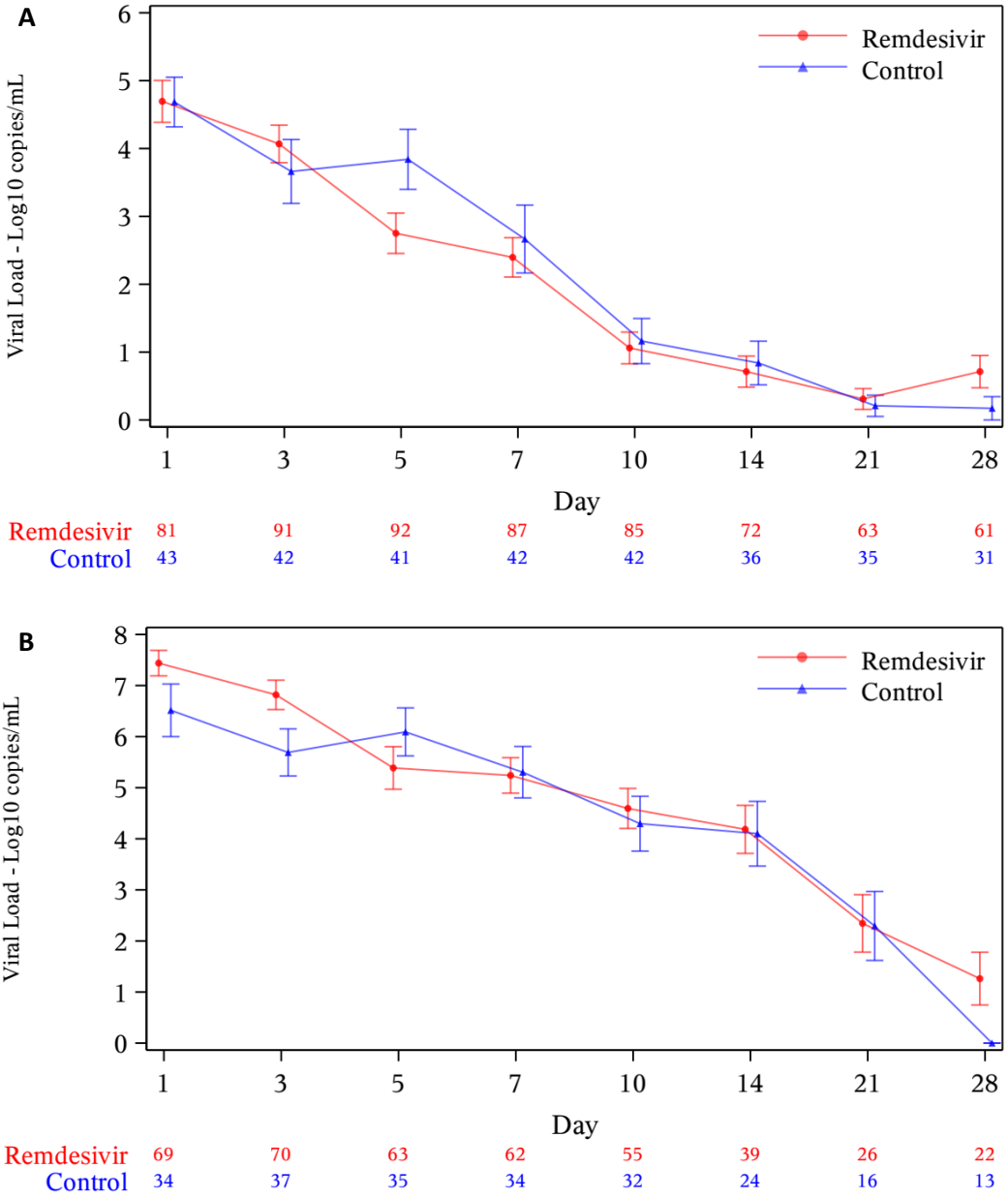
Figure 2. Kaplan Meier of time-to-clinical improvement in the Intention-to-Treat Population during the 28 days.



No. at risk								
Remdesivir	158	155	147	123	101	82	63	25
Control	78	78	75	64	52	46	38	17

Note. Benefit ratio (BR) for clinical improvement was 1.23; 95% confidence interval [CI], 0.87 to 1.75; The adjusted BR for randomization stratification was 1.25; 95% CI 0.88 to 1.78.

Figure 3. SARS-CoV-2 load by qPCR on the upper (nasopharyngeal or oropharyngeal swabs) (Panel A) /lower (Panel B) respiratory tract specimens (data only from viral positive population).



Data were presented mean (±SE). Results less than the lower limit of quantification of PCR assay and greater than the limit of qualitative detection are imputed with half of actual value log10 copies/mL; results of patients with viral negative RNA are imputed with 0 $\log_{10}$ copies/mL.