

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

ABSTRACT

BACKGROUND

Although several therapeutic agents have been evaluated for the treatment of coronavirus disease 2019 (Covid-19), none have yet been shown to be efficacious.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19 with evidence of lower respiratory tract involvement. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only.

RESULTS

A total of 1063 patients underwent randomization. The data and safety monitoring board recommended early unblinding of the results on the basis of findings from an analysis that showed shortened time to recovery in the remdesivir group. Preliminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo) with data available after randomization indicated that those who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; $P < 0.001$). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%).

CONCLUSIONS

Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Beigel at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Ln., Rm. 7E60, MSC 9826, Rockville, MD 20892-9826, or at jbeigel@niaid.nih.gov.

*A complete list of members of the ACTT-1 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 22, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2007764

Copyright © 2020 Massachusetts Medical Society.

A NOVEL CORONAVIRUS, SEVERE ACUTE respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December 2019 as the cause of a respiratory illness designated coronavirus disease 2019, or Covid-19.¹ Several therapeutic agents have been evaluated for the treatment of Covid-19, but none have yet been shown to be efficacious.^{2,3} Remdesivir (GS-5734), an inhibitor of the viral RNA-dependent, RNA polymerase with inhibitory activity against SARS-CoV and the Middle East respiratory syndrome (MERS-CoV),^{4,7} was identified early as a promising therapeutic candidate for Covid-19 because of its ability to inhibit SARS-CoV-2 *in vitro*.⁸ In addition, in nonhuman primate studies, remdesivir initiated 12 hours after inoculation with MERS-CoV^{9,10} reduced lung virus levels and lung damage.

To evaluate the clinical efficacy and safety of putative investigational therapeutic agents among hospitalized adults with laboratory-confirmed Covid-19, we designed an adaptive platform to rapidly conduct a series of phase 3, randomized, double-blind, placebo-controlled trials. Here, we describe the preliminary results of the first stage of the Adaptive Covid-19 Treatment Trial (ACTT-1), in which we evaluated treatment with remdesivir as compared with placebo.

METHODS

DESIGN

Enrollment for ACTT-1 began on February 21, 2020, and ended on April 19, 2020. There were 60 trial sites and 13 subsites in the United States (45 sites), Denmark (8), the United Kingdom (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), and Singapore (1). Eligible patients were randomly assigned in a 1:1 ratio to receive either remdesivir or placebo. Randomization was stratified by study site and disease severity at enrollment (see the Supplementary Appendix, available with the full text of this article at NEJM.org, for details about stratification criteria). Remdesivir was administered intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death. A matching placebo was administered according to the same schedule and in the same volume as the active drug. A normal saline placebo was used at the European sites and at some

non-European sites owing to a shortage of matching placebo; the infusions were masked with an opaque bag and tubing covers to maintain blinding. All patients received supportive care according to the standard of care for the trial site hospital. If a hospital had a written policy or guideline for use of other treatments for Covid-19, patients could receive those treatments. In the absence of a written policy or guideline, other experimental treatment or off-label use of marketed medications intended as specific treatment for Covid-19 were prohibited from day 1 through day 29 (though such medications could have been used before enrollment in this trial).

The trial protocol was approved by the institutional review board at each site (or by a centralized institutional review board as applicable) and was overseen by an independent data and safety monitoring board. Informed consent was obtained from each patient or from the patient's legally authorized representative if the patient was unable to provide consent. Full details of the trial design, conduct, oversight, and analyses can be found in the protocol and statistical analysis plan (available at NEJM.org).

PROCEDURES

Patients were assessed daily during their hospitalization, from day 1 through day 29. The patient's clinical status on an eight-category ordinal scale (defined below) and the National Early Warning Score was recorded each day.^{11,12} All serious adverse events and grade 3 or 4 adverse events that represented an increase in severity from day 1 and any grade 2 or higher suspected drug-related hypersensitivity reactions were recorded. (See the full description of trial procedures in the Supplementary Appendix.)

STATISTICAL ANALYSIS

The primary analysis was a stratified log-rank test of the time to recovery with remdesivir as compared with placebo, with stratification by disease severity. (See the Supplementary Appendix for more information about the planned statistical analysis.)

The primary outcome measure was the time to recovery, defined as the first day, during the 28 days after enrollment, on which a patient satisfied categories 1, 2, or 3 on the eight-category ordinal scale. The categories are as follows: 1, not hospitalized, no limitations of activities;

2, not hospitalized, limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19-related or other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8, death. Other outcomes included mortality at 14 and 28 days after enrollment and grade 3 and 4 adverse events and serious adverse events that occurred during the trial. Prespecified subgroups in these analyses were defined according to sex, disease severity (as defined for stratification and by ordinal scale at enrollment), age (18 to 39 years, 40 to 64 years, or 65 years of age or older), and duration of symptoms before randomization (≤ 10 days or >10 days). (See the protocol for more information about the trial methods.)

The primary outcome was initially defined as the difference in clinical status, defined by the eight-category ordinal scale, among patients treated with remdesivir as compared with placebo at day 15. This initial primary outcome became the key secondary outcome after the change in primary outcome. The change was proposed on March 22, 2020, by trial statisticians who were unaware of treatment assignments and had no knowledge of outcome data. When this change was proposed, 72 patients had been enrolled and no interim data were available. The amendment was finalized on April 2, 2020, without any knowledge of outcome data from the trial and before any interim data were available. This change in primary outcome was made in response to evolving information, external to the trial, indicating that Covid-19 may have a more protracted course than previously appreciated.

On April 27, 2020, the data and safety monitoring board reviewed results. Although this review was originally planned as an interim analysis, because of the rapid pace of enrollment, the review occurred after completion of enrollment while follow-up was still ongoing. At the time of the data and safety monitoring board report, which was based on data cutoff date of April 22, 2020, a total of 482 recoveries (exceeding the

estimated number of recoveries needed for the trial) and 81 deaths had been entered in the database. At that time, the data and safety monitoring board recommended that the preliminary primary analysis report and mortality data from the closed safety report be provided to trial team members from the National Institute of Allergy and Infectious Diseases (NIAID). These results were subsequently made public; the treating physician could request to be made aware of the treatment assignment of patients who had not completed day 29 if clinically indicated (e.g., because of worsening clinical status), and patients originally in the placebo group could be given remdesivir. This report summarizes the preliminary results from this ongoing trial.

RESULTS

PATIENTS

Of the 1107 patients who were assessed for eligibility, 1063 underwent randomization; 541 were assigned to the remdesivir group and 522 to the placebo group (Fig. 1). Of those assigned to receive remdesivir, 531 patients (98.2%) received the treatment as assigned. Forty-nine patients had remdesivir treatment discontinued before day 10 because of an adverse event or a serious adverse event other than death (36 patients) or because the patient withdrew consent (13). Of those assigned to receive placebo, 518 patients (99.2%) received placebo as assigned. Fifty-three patients discontinued placebo before day 10 because of an adverse event or a serious adverse event other than death (36 patients), because the patient withdrew consent (15), or because the patient was found to be ineligible for trial enrollment (2).

As of April 28, 2020, a total of 391 patients in the remdesivir group and 340 in the placebo group had completed the trial through day 29, recovered, or died. Eight patients who received remdesivir and 9 who received placebo terminated their participation in the trial before day 29. There were 132 patients in the remdesivir group and 169 in the placebo group who had not recovered and had not completed the day 29 follow-up visit. The analysis population included 1059 patients for whom we have at least some postbaseline data available (538 in the remdesivir group and 521 in the placebo group). Four of the 1063 patients were not included in the pri-

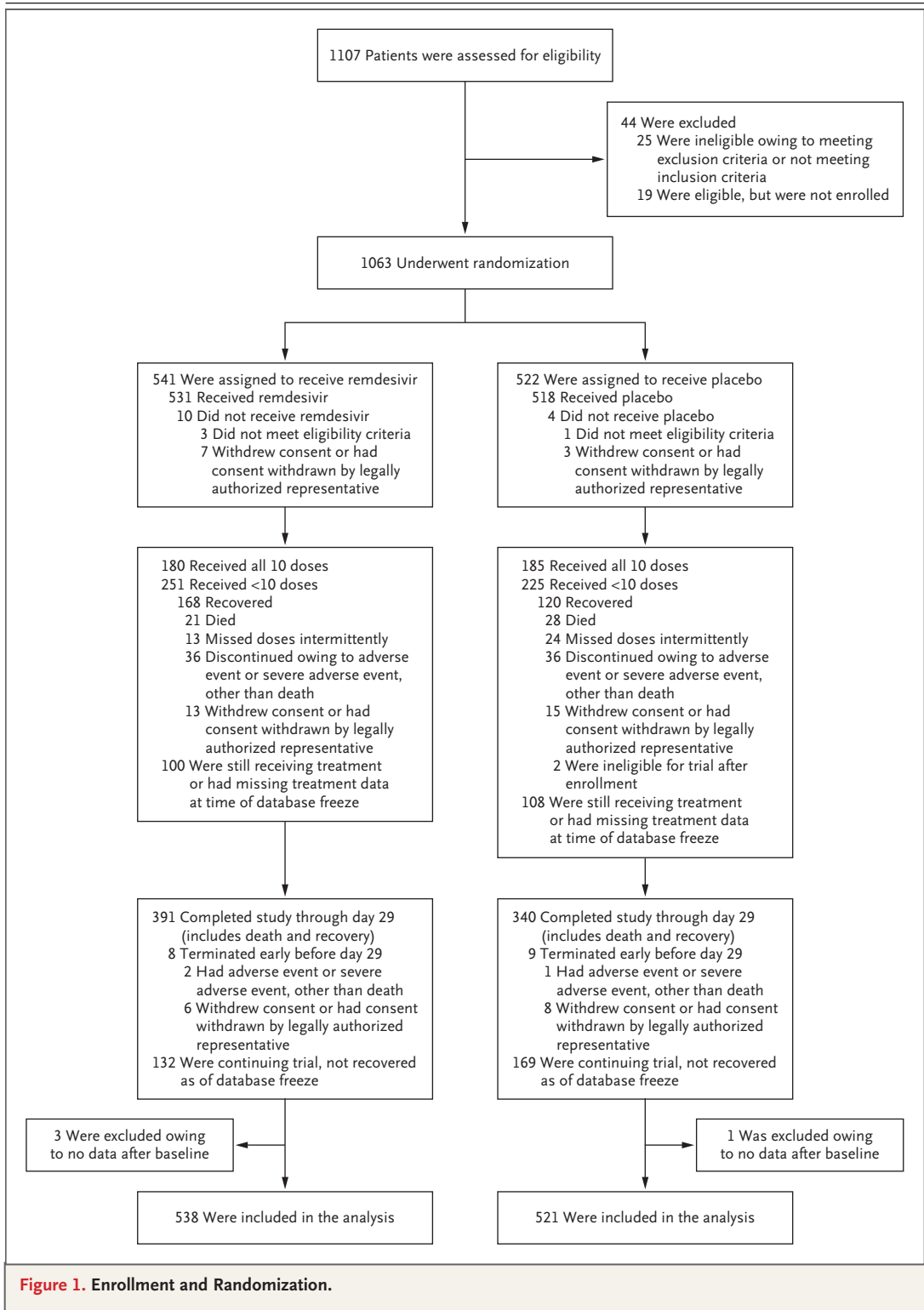


Figure 1. Enrollment and Randomization.

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	All (N=1063)	Remdesivir (N=541)	Placebo (N=522)
Age — yr	58.9±15.0	58.6±14.6	59.2±15.4
Male sex — no. (%)	684 (64.3)	352 (65.1)	332 (63.6)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	7 (0.7)	4 (0.7)	3 (0.6)
Asian	134 (12.6)	77 (14.2)	57 (10.9)
Black or African American	219 (20.6)	108 (20.0)	111 (21.3)
White	565 (53.2)	279 (51.6)	286 (54.8)
Hispanic or Latino — no. (%)	249 (23.4)	132 (24.4)	117 (22.4)
Median time (IQR) from symptom onset to randomization — days‡	9 (6–12)	9 (6–12)	9 (7–13)
No. of coexisting conditions — no. /total no. (%)‡			
None	193/920 (21.0)	91/467 (19.5)	102/453 (22.5)
One	248/920 (27.0)	131/467 (28.1)	117/453 (25.8)
Two or more	479/920 (52.1)	245/467 (52.5)	234/453 (51.7)
Coexisting conditions — no./total no. (%)			
Hypertension	460/928 (49.6)	231/469 (49.3)	229/459 (49.9)
Obesity	342/925 (37.0)	177/469 (37.7)	165/456 (36.2)
Type 2 diabetes	275/927 (29.7)	144/470 (30.6)	131/457 (28.7)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	127 (11.9)	67 (12.4)	60 (11.5)
5. Hospitalized, requiring supplemental oxygen	421 (39.6)	222 (41.0)	199 (38.1)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	197 (18.5)	98 (18.1)	99 (19.0)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	272 (25.6)	125 (23.1)	147 (28.2)
Baseline score missing	46 (4.3)	29 (5.4)	17 (3.3)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range. The full table of baseline characteristics is available in the Supplementary Appendix.

† Race and ethnic group were reported by the patients. The number of patients in other races and ethnic groups are listed in Table S1 in the Supplementary Appendix.

‡ As of April 28, 2020, data on symptom onset were missing for 15 patients; data on coexisting conditions were missing for 133 patients and were incomplete for 10 patients.

mary analysis because no postbaseline data were available at the time of the database freeze.

The mean age of patients was 58.9 years, and 64.3% were male (Table 1). On the basis of the evolving epidemiology of Covid-19 during the trial, 79.8% of patients were enrolled at sites in North America, 15.3% in Europe, and 4.9% in Asia (Table S1). Overall, 53.2% of the patients were white, 20.6% were black, 12.6% were Asian, and 13.6% were designated as other or not reported; 249 (23.4%) were Hispanic or Latino. Most pa-

tients had either one (27.0%) or two or more (52.1%) of the prespecified coexisting conditions at enrollment, most commonly hypertension (49.6%), obesity (37.0%), and type 2 diabetes mellitus (29.7%).

The median number of days between symptom onset and randomization was 9 (interquartile range, 6 to 12). Nine hundred forty-three (88.7%) patients had severe disease at enrollment as defined in the Supplementary Appendix; 272 (25.6%) patients met category 7 criteria on

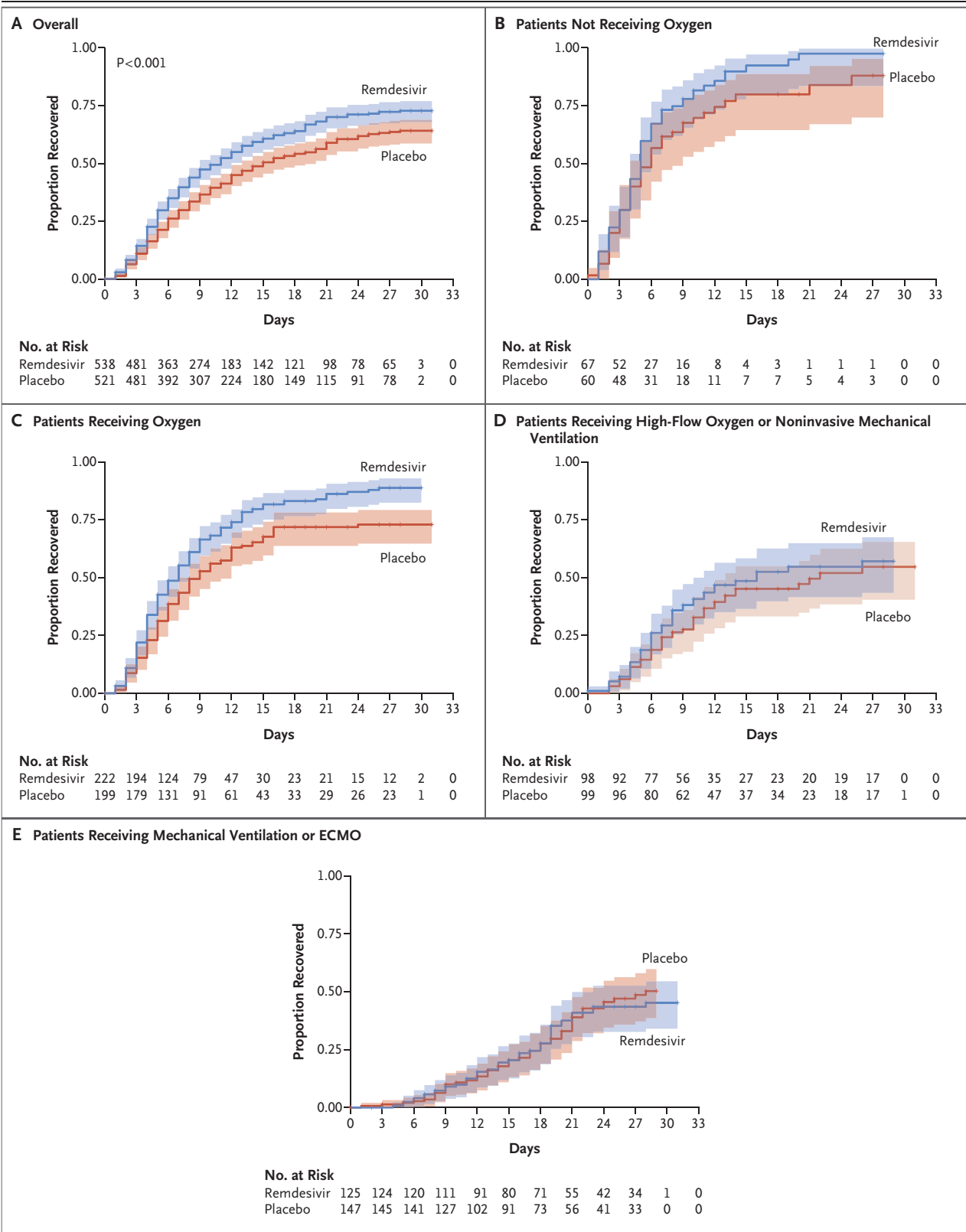


Figure 2 (facing page). Kaplan–Meier Estimates of Cumulative Recoveries.

Cumulative recovery estimates are shown in the overall population (Panel A), in patients with a baseline score of 4 on the ordinal scale (not receiving oxygen; Panel B), in those with a baseline score of 5 (receiving oxygen; Panel C), in those with a baseline score of 6 (receiving high-flow oxygen or noninvasive mechanical ventilation; Panel D), and in those with a baseline score of 7 (receiving mechanical ventilation or ECMO; Panel E).

the ordinal scale, 197 (18.5%) category 6, 421 (39.6%) category 5, and 127 (11.9%) category 4. There were 46 (4.3%) patients who had missing ordinal scale data at enrollment. No substantial imbalances in baseline characteristics were observed between the remdesivir group and the placebo group.

PRIMARY OUTCOME

Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 11 days, as compared with 15 days; rate ratio for recovery, 1.32; 95% confidence interval [CI], 1.12 to 1.55; $P < 0.001$; 1059 patients (Fig. 2 and Table 2). Among patients with a baseline ordinal score of 5 (421 patients), the rate ratio for recovery was 1.47 (95% CI, 1.17 to 1.84); among patients with a baseline score of 4 (127 patients) and those with a baseline score of 6 (197 patients), the rate ratio estimates for recovery were 1.38 (95% CI, 0.94 to 2.03) and 1.20 (95% CI, 0.79 to 1.81), respectively. For those receiving mechanical ventilation or ECMO at enrollment (baseline ordinal scores of 7; 272 patients), the rate ratio for recovery was 0.95 (95% CI, 0.64 to 1.42). A test of interaction of treatment with baseline score on the ordinal scale was not significant. An analysis adjusting for baseline ordinal score as a stratification variable was conducted to evaluate the overall effect (of the percentage of patients in each ordinal score category at baseline) on the primary outcome. This adjusted analysis produced a similar treatment-effect estimate (rate ratio for recovery, 1.31; 95% CI, 1.12 to 1.54; 1017 patients). Table S2 in the Supplementary Appendix shows results according to the baseline severity stratum of mild-to-moderate as compared with severe. Patients who underwent randomization during the first 10 days after the onset of

symptoms had a rate ratio for recovery of 1.28 (95% CI, 1.05 to 1.57; 664 patients), whereas patients who underwent randomization more than 10 days after the onset of symptoms had a rate ratio for recovery of 1.38 (95% CI, 1.05 to 1.81; 380 patients) (Fig. 3).

KEY SECONDARY OUTCOME

The odds of improvement in the ordinal scale score were higher in the remdesivir group, as determined by a proportional odds model at the day 15 visit, than in the placebo group (odds ratio for improvement, 1.50; 95% CI, 1.18 to 1.91; $P = 0.001$; 844 patients) (Table 2 and Fig. S5). Mortality was numerically lower in the remdesivir group than in the placebo group, but the difference was not significant (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04; 1059 patients). The Kaplan–Meier estimates of mortality by 14 days were 7.1% and 11.9% in the remdesivir and placebo groups, respectively (Table 2). The Kaplan–Meier estimates of mortality by 28 days are not reported in this preliminary analysis, given the large number of patients that had yet to complete day 29 visits. An analysis with adjustment for baseline ordinal score as a stratification variable showed a hazard ratio for death of 0.74 (95% CI, 0.50 to 1.10).

SAFETY OUTCOMES

Serious adverse events occurred in 114 patients (21.1%) in the remdesivir group and 141 patients (27.0%) in the placebo group (Table S3); 4 events (2 in each group) were judged by site investigators to be related to remdesivir or placebo. There were 28 serious respiratory failure adverse events in the remdesivir group (5.2% of patients) and 42 in the placebo group (8.0% of patients). Acute respiratory failure, hypotension, viral pneumonia, and acute kidney injury were slightly more common among patients in the placebo group. No deaths were considered to be related to treatment assignment, as judged by the site investigators.

Grade 3 or 4 adverse events occurred in 156 patients (28.8%) in the remdesivir group and in 172 in the placebo group (33.0%) (Table S4). The most common adverse events in the remdesivir group were anemia or decreased hemoglobin (43 events [7.9%], as compared with 47 [9.0%] in the placebo group); acute kidney injury, decreased estimated glomerular filtration rate or creatinine clearance, or increased blood creatinine (40

Table 2. Outcomes Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population.*

	Overall†									
	4		5		6		7			
	Remdesivir (N=538)	Placebo (N=521)	Remdesivir (N=67)	Placebo (N=60)	Remdesivir (N=222)	Placebo (N=199)	Remdesivir (N=98)	Placebo (N=99)	Remdesivir (N=125)	Placebo (N=147)
Recovery										
No. of recoveries	334	273	61	47	177	128	47	43	45	51
Median time to recovery (95% CI) — days	11 (9–12)	15 (13–19)	5 (4–6)	6 (4–8)	7 (6–8)	9 (7–11)	16 (NE–10)	22 (NE–12)	NE–NE	28 (NE–22)
Rate ratio (95% CI) †	1.32 (1.12–1.55 [P<0.001])		1.38 (0.94–2.03)		1.47 (1.17–1.84)		1.20 (0.79–1.81)		0.95 (0.64–1.42)	
Mortality										
Hazard ratio (95% CI)	0.70 (0.47–1.04)		0.46 (0.04–5.08)		0.22 (0.08–0.58)		1.12 (0.53–2.38)		1.06 (0.59–1.92)	
No. of deaths by day 14	32	54	1	1	4	19	13	13	13	19
Kaplan–Meier estimate — % (95% CI)	7.1 (5.0–9.9)	11.9 (9.2–15.4)	1.5 (0.2–10.1)	2.5 (0.4–16.5)	2.4 (0.9–6.4)	10.9 (7.1–16.7)	15.2 (9.0–25.0)	14.7 (8.7–24.3)	11.3 (6.7–18.8)	14.1 (9.2–21.2)
Ordinal score at day 15 (±2 days) — no. (%):‡										
Patients with baseline and day 15 score data — no.	434	410	60	51	196	161	71	77	101	115
1	99 (22.8)	76 (18.5)	22 (36.7)	15 (29.4)	54 (27.6)	45 (28.0)	13 (18.3)	7 (9.1)	10 (9.9)	8 (7.0)
2	158 (36.4)	127 (31.0)	25 (41.7)	21 (41.2)	95 (48.5)	66 (41.0)	28 (39.4)	27 (35.1)	6 (5.9)	10 (8.7)
3	11 (2.5)	6 (1.5)	7 (11.7)	4 (7.8)	4 (2.0)	2 (1.2)	0	0	0	0
4	23 (5.3)	20 (4.9)	1 (1.7)	3 (5.9)	12 (6.1)	7 (4.3)	4 (5.6)	4 (5.2)	6 (5.9)	6 (5.2)
5	34 (7.8)	40 (9.8)	3 (5.0)	5 (9.8)	14 (7.1)	6 (3.7)	2 (2.8)	7 (9.1)	15 (14.9)	22 (19.1)
6	16 (3.7)	14 (3.4)	1 (1.7)	0 (0)	1 (0.5)	3 (1.9)	6 (8.5)	6 (7.8)	7 (6.9)	5 (4.3)
7	60 (13.8)	72 (17.6)	0 (0)	2 (3.9)	12 (6.1)	12 (7.5)	5 (7.0)	13 (16.9)	43 (42.6)	45 (39.1)
8	33 (7.6)	55 (13.4)	1 (1.7)	1 (2.0)	4 (2.0)	20 (12.4)	13 (18.3)	13 (16.9)	14 (13.9)	19 (16.5)
Odds ratio (95% CI)	1.50 (1.18–1.91 [P=0.001])		1.51 (0.76–3.00)		1.31 (0.89–1.92)		1.60 (0.89–2.86)		1.04 (0.64–1.68)	

* P values and confidence intervals have not been adjusted for multiple comparisons. NE denotes not possible to estimate.
 † Recovery rate ratios and hazard ratios were calculated from the stratified Cox model; P values for these ratios were calculated with the stratified log-rank test. Recovery rate ratios greater than 1 indicate a benefit for remdesivir; hazard ratios less than 1 indicate a benefit for remdesivir.
 ‡ The ordinal score at day 15 is the patient's worst score on the ordinal scale during the previous day. In the remdesivir group, 103 patients did not have ordinal scale scores for the day 15 visit at the time of the data freeze (11 with mild-to-moderate illness and 92 with severe illness). In the placebo group, 109 patients did not have ordinal scale scores for the day 15 visit at the time of the data freeze (12 with mild-to-moderate illness and 97 with severe illness). Two patients died 15 days after randomization and are included in the ordinal scale scores but not in the estimate of mortality by day 14. Scores on the ordinal scale are as follows: 1, not hospitalized, no limitations of activities; 2, not hospitalized, limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8, death. Odds ratios and P values were calculated with the use of a proportional odds model. Odds ratio values greater than 1 indicate a benefit for remdesivir.

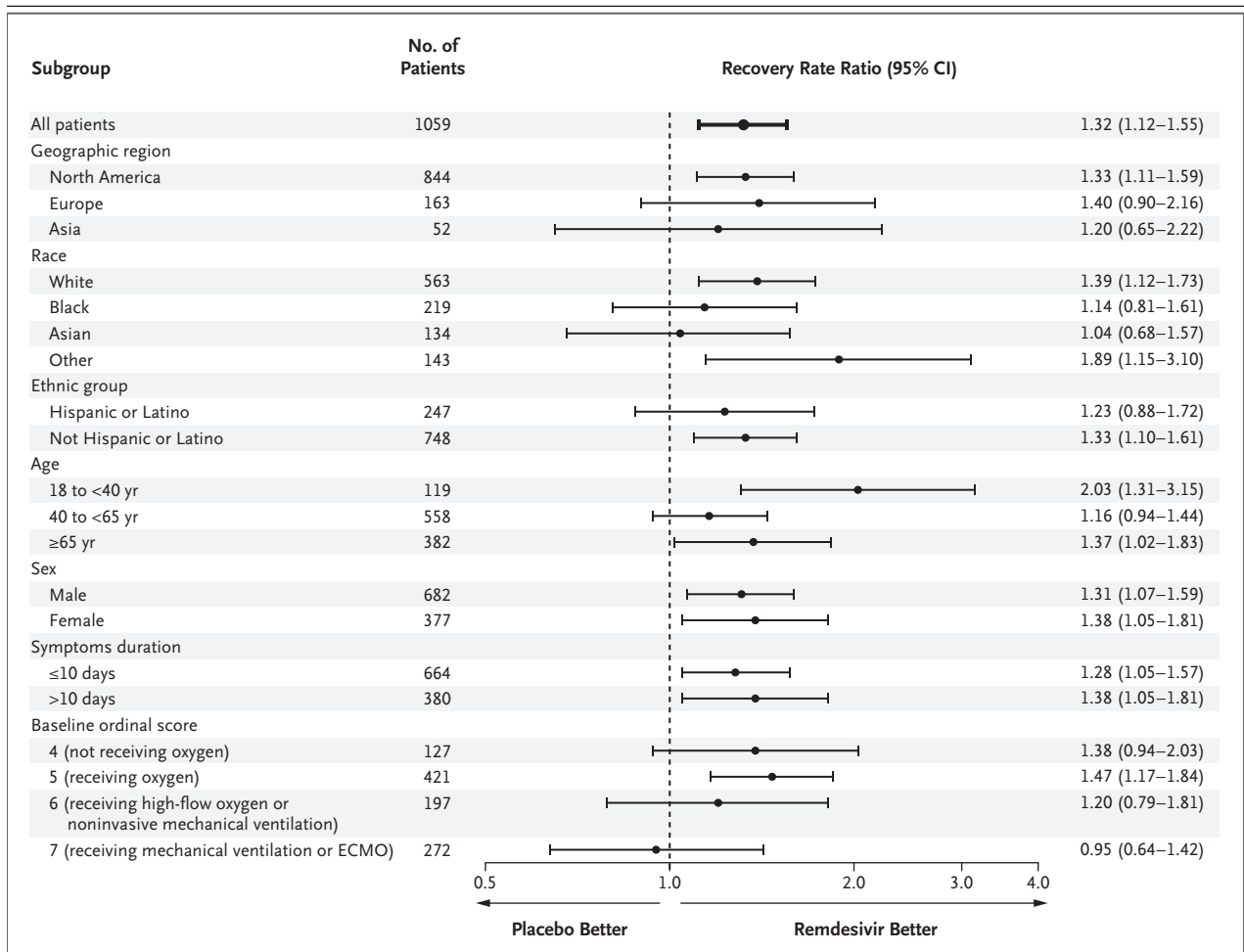


Figure 3. Time to Recovery According to Subgroup.

The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects. Race and ethnic group were reported by the patients.

events [7.4%], as compared with 38 [7.3%]); pyrexia (27 events [5.0%], as compared with 17 [3.3%]); hyperglycemia or increased blood glucose level (22 events [4.1%], as compared with 17 [3.3%]); and increased aminotransferase levels including alanine aminotransferase, aspartate aminotransferase, or both (22 events [4.1%], as compared with 31 [5.9%]). Otherwise, the incidence of adverse events was not found to be significantly different between the remdesivir group and the placebo group.

DISCUSSION

Preliminary results of this trial suggest that a 10-day course of remdesivir was superior to placebo

in the treatment of hospitalized patients with Covid-19. This benefit was seen in the number of days to recovery (median, 11 days, as compared with 15; rate ratio for recovery, 1.32 [95% CI, 1.12 to 1.55]) and in recovery according to the ordinal scale score at day 15 (odds ratio, 1.50; 95% CI, 1.18 to 1.91). Even though the trial was ongoing, the data and safety monitoring board made the recommendation to unblind the results to the trial team members from the NIAID, who subsequently decided to make the results public. Given the strength of the results about remdesivir, these findings were deemed to be of immediate importance for the care of patients still participating in the trial as well as for those outside the trial who might benefit from treatment with remdesivir.

The benefit was most apparent in patients with a baseline ordinal score of 5 (requiring oxygen), a finding most likely due to the larger sample size in this category (since the interaction test of treatment by baseline score on the ordinal scale was not significant). Confidence intervals for baseline ordinal scores of 4 (not receiving oxygen), 6 (receiving high-flow oxygen), and 7 (receiving ECMO or mechanical ventilation) are wide. We note that the median recovery time for patients in category 7 could not be estimated, which suggests that the follow-up time may have been too short to evaluate this subgroup. Additional analyses of outcomes such as the time to a one- or two-point improvement on the ordinal scale score will be conducted after the full cohort has completed 28 days of follow-up and may provide additional insight into the treatment of this critical subgroup. Our findings highlight the need to identify Covid-19 cases and start antiviral treatment before the pulmonary disease progresses to require mechanical ventilation.

The findings in our trial should be compared with those observed in a randomized trial from China in which 237 patients were enrolled (158 assigned to remdesivir and 79 to placebo).¹³ The time to clinical improvement, defined as the time to a two-point improvement in the score on the ordinal scale, was 21.0 days (95% CI, 13.0 to 28.0) in the remdesivir group and 23.0 days (95% CI, 15.0 to 28.0) in the control group, with a hazard ratio (for clinical improvement) of 1.23 (95% CI, 0.87 to 1.75). The six-category ordinal scale used in that trial yielded a common odds ratio for improvement in the ordinal score scale of 1.25 (95% CI, 0.76 to 2.04) at day 14. That trial failed to complete full enrollment (owing to the end of the outbreak), had lower power than the present trial (owing to the smaller sample size and a 2:1 randomization), and was unable to demonstrate any statistically significant clinical benefits of remdesivir.

The primary outcome of the current trial was changed with protocol version 3 on April 2, 2020, from a comparison of the eight-category ordinal scale scores on day 15 to a comparison of time to recovery up to day 29. Little was known about the natural clinical course of Covid-19 when the trial was designed in February 2020. Emerging data suggested that Covid-19 had a more protracted course than was previ-

ously known, which aroused concern that a difference in outcome after day 15 would have been missed by a single assessment at day 15. The amendment was proposed on March 22, 2020, by trial statisticians who were unaware of treatment assignment and had no knowledge of outcome data; when this change was proposed 72 patients had been enrolled. Although changes in the primary outcome are not common for diseases that are well understood, it is recognized that in some trials, such as those involving poorly understood diseases, circumstances may require a change in the way an outcome is assessed or may necessitate a different outcome.¹⁴ The original primary outcome became the key secondary end point. In the end, findings for both primary and key secondary end points were significantly different between the remdesivir and placebo groups.

Numerous challenges were encountered during this trial. The trial was implemented during a time of restricted travel, and hospitals restricted the entrance of nonessential personnel. Training, site initiation visits, and monitoring visits often were performed remotely. Research staff were often assigned other clinical duties, and staff illnesses strained research resources. Many sites did not have adequate supplies of personal protective equipment and trial-related supplies, such as swabs. However, research teams were motivated to find creative solutions to overcome these challenges.

The Food and Drug Administration has made remdesivir available under an emergency-use authorization for the treatment of adults and children with severe Covid-19 disease. Our preliminary report is intended to help inform clinicians considering the use of remdesivir. We are awaiting final visits, data entry, monitoring, and data lock for the last of the 1063 patients enrolled, after which an update of the results will be provided. To ensure the accuracy of the reported findings, we evaluated the primary outcome, key secondary outcomes, and mortality results on current data from May 18, 2020. The results were similar to those reported in the Results section of this article. The full statistical analysis of the entire trial population must occur, in order to fully understand the efficacy of remdesivir in this trial.

These preliminary findings support the use of remdesivir for patients who are hospitalized

with Covid-19 and require supplemental oxygen therapy. However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient. Future strategies should evaluate antiviral agents in combination with other therapeutic approaches or combinations of antiviral agents to continue to improve patient outcomes in Covid-19.

The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, the Uniformed Services University of the Health Sciences, the Henry M. Jackson Foundation for the Advancement of Military Medicine, the Departments of the Army, Navy, or Air Force, the Department of Defense, or the Department of Veterans Affairs, nor does any mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. Gilead Sciences provided remdesivir for use in this trial but did not provide any financial support. Employees of Gilead Sciences participated in discussions about protocol development and in weekly protocol team calls. The NIAID ultimately made all decisions regarding trial design and implementation.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

The trial was sponsored and primarily funded by the

National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, MD. This trial has been funded in part with federal funds from the NIAID and the National Cancer Institute, NIH, under contract HHSN261200800001E 75N910D00024, task order number 75N91019F00130/75N91020F00010, and by the Department of Defense, Defense Health Program. This trial has been supported in part by the NIAID of the NIH under award numbers UM1AI148684, UM1AI148576, UM1AI148573, UM1AI148575, UM1AI148452, UM1AI148685, UM1AI148450, and UM1AI148689. The trial has also been funded in part by the governments of Japan, Mexico, Denmark, and Singapore. The trial site in South Korea received funding from the Seoul National University Hospital. Support for the London International Coordinating Centre was also provided by the United Kingdom Medical Research Council (MRC_UU_12023/23).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the members of the ACTT-1 Study Team (see the Supplementary Appendix) for their many contributions in conducting the trial, the members of the Data and Safety Monitoring Board (Michael G. Ison, M.D. [Chair], Northwestern University Feinberg School of Medicine; Nina Singh, M.D., University of Pittsburgh; Bernd Salzberger, M.D., Ph.D., University of Regensburg; Wendy Leisenring, Sc.D., Fred Hutchinson Cancer Research Center; and Peter Sasieni, Ph.D., King's College London) for their oversight, and the patients themselves for their altruism in participating in this trial.

APPENDIX

The authors' full names and academic degrees are as follows: John H. Beigel, M.D., Kay M. Tomashek, M.D., M.P.H., Lori E. Dodd, Ph.D., Aneesh K. Mehta, M.D., Barry S. Zingman, M.D., Andre C. Kalil, M.D., M.P.H., Elizabeth Hohmann, M.D., Helen Y. Chu, M.D., M.P.H., Annie Luetkemeyer, M.D., Susan Kline, M.D., M.P.H., Diego Lopez de Castilla, M.D., M.P.H., Robert W. Finberg, M.D., Kerry Dierberg, M.D., M.P.H., Victor Tapson, M.D., Lanny Hsieh, M.D., Thomas F. Patterson, M.D., Roger Paredes, M.D., Ph.D., Daniel A. Sweeney, M.D., William R. Short, M.D., M.P.H., Giota Touloumi, Ph.D., David Chien Lye, M.B., B.S., Norio Ohmagari, M.D., Ph.D., Myoung-don Oh, M.D., Guillermo M. Ruiz-Palacios, M.D., Thomas Benfield, M.D., Gerd Fätkenheuer, M.D., Mark G. Kortepeter, M.D., Robert L. Atmar, M.D., C. Buddy Creech, M.D., M.P.H., Jens Lundgren, M.D., Abdel G. Babiker, Ph.D., Sarah Pett, Ph.D., James D. Neaton, Ph.D., Timothy H. Burgess, M.D., M.P.H., Tyler Bonnett, M.S., Michelle Green, M.P.H., M.B.A., Mat Makowski, Ph.D., Anu Osinusi, M.D., M.P.H., Seema Nayak, M.D., and H. Clifford Lane, M.D.

The authors' affiliations are as follows: the National Institute of Allergy and Infectious Diseases, National Institutes of Health (J.H.B., K.M.T., L.E.D., S.N., H.C.L.), and the Infectious Disease Clinical Research Program, Uniformed Services University of the Health Sciences (T.H.B.), Bethesda, the Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research, Frederick (T. Bonnett), and Emmes, Rockville (M.G., M.M.) — all in Maryland; Emory University, Atlanta (A.K.M.); Montefiore Medical Center—Albert Einstein College of Medicine (B.S.Z.) and NYU Langone Health and NYC Health + Hospitals—Bellevue (K.D.), New York; University of Nebraska Medical Center, Omaha (A.C.K., M.G.K.); Massachusetts General Hospital, Boston (E.H.), and University of Massachusetts Medical School, Worcester (R.W.F.); University of Washington, Seattle (H.Y.C.), and Evergreen Health Medical Center, Kirkland (D.L.C.) — both in Washington; University of California, San Francisco, San Francisco (A.L.), Cedars Sinai Medical Center, Los Angeles (V.T.), University of California, Irvine, Irvine (L.H.), University of California, San Diego, La Jolla (D.A.S.), and Gilead Sciences, Foster City (A.O.) — all in California; University of Minnesota (S.K.) and University of Minnesota, School of Public Health and INSIGHT (J.D.N.), Minneapolis; University of Texas Health San Antonio, University Health System, and the South Texas Veterans Health Care System, San Antonio (T.F.P.), and Baylor College of Medicine, Houston (R.L.A.); Hospital Germans Trias i Pujol & IrsiCaixa AIDS Research Institute, Badalona, Spain (R.P.); University of Pennsylvania, Philadelphia (W.R.S.); Medical School, National and Kapodistrian University of Athens, Athens (G.T.); National Center for Infectious Diseases—Tan Tock Seng Hospital—Lee Kong Chian School of Medicine—Yong Loo Lin School of Medicine, Singapore, Singapore (D.C.L.); the National Center for Global Health and Medicine Hospital, Tokyo (N.O.); Seoul National University Hospital, Seoul, South Korea (M.O.); Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City (G.M.R.-P.); the Department of Infectious Diseases, Amager Hvidovre Hospital—University of Copenhagen, Hvidovre (T. Benfield), and Rigshospitalet, Department of Infectious Diseases (CHIP) and INSIGHT, Copenhagen (J.L.) — both in Denmark; University Hospital of Cologne, Cologne, Germany (G.F.); Vanderbilt University Medical Center, Nashville (C.B.C.); and University College London, MRC Clinical Trials Unit at UCL and INSIGHT, London (A.G.B., S.P.).

REFERENCES

1. Helmy YA, Fawzy M, Elawad A, Sobieh A, Kenney SP, Shehata AA. The COVID-19 pandemic: a comprehensive review of taxonomy, genetics, epidemiology, diagnosis, treatment, and control. *J Clin Med* 2020;9(4):E1225.
2. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020; 382:1787-99.
3. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open* 2020;3(4): e208857.

4. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020;11:222.
5. Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *mBio* 2018;9(2):e00221-18.
6. Brown AJ, Won JJ, Graham RL, et al. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. *Antiviral Res* 2019;169:104541.
7. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med* 2017;9:eaal3653.
8. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;30:269-71.
9. de Wit E, Rasmussen AL, Falzarano D, et al. Middle East respiratory syndrome coronavirus (MERS-CoV) causes transient lower respiratory tract infection in rhesus macaques. *Proc Natl Acad Sci U S A* 2013;110:16598-603.
10. de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A* 2020;117:6771-6.
11. Royal College of Physicians. National Early Warning Score (NEWS) 2. 2017 (<https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2>).
12. King JC, Beigel JH, Ison MG, et al. Clinical development of therapeutic agents for hospitalized patients with influenza: challenges and innovations. *Open Forum Infect Dis* 2019;6:ofz137.
13. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020;395:1569-78.
14. The CONSORT Group. 3b. Changes to trial design (<http://www.consort-statement.org/consort-2010>).

Copyright © 2020 Massachusetts Medical Society.