Remdesivir (trade name: Veklury) Most likely ineffective for COVID-19

MedCheck Editorial team

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Animal experiment(1)：

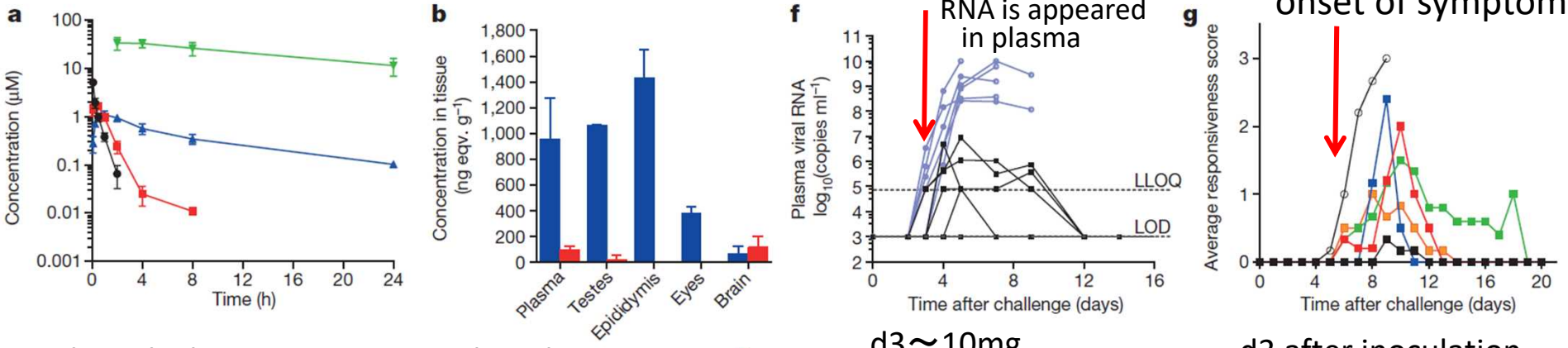
Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys

If enough remdesivir is administered before the onset of symptoms it reduced mortality. No test in which it was administered after the onset of symptoms was done.

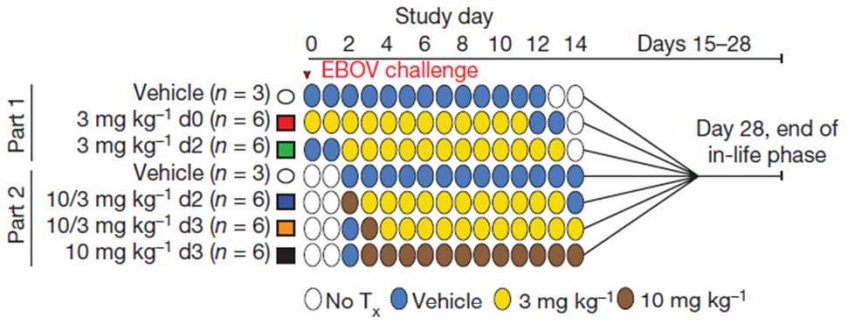
4) Warren TK et al. Nature 2016;531:381-5.

d3 after inoculation
RNA is appeared
in plasma

d5 after inoculation
onset of symptom



c d0 ：Ebola virus was inoculated i.m.



d3～10mg
d310mg,d4～3mg
d2～3mg
d0～3mg
d210mg,d3～3mg
control

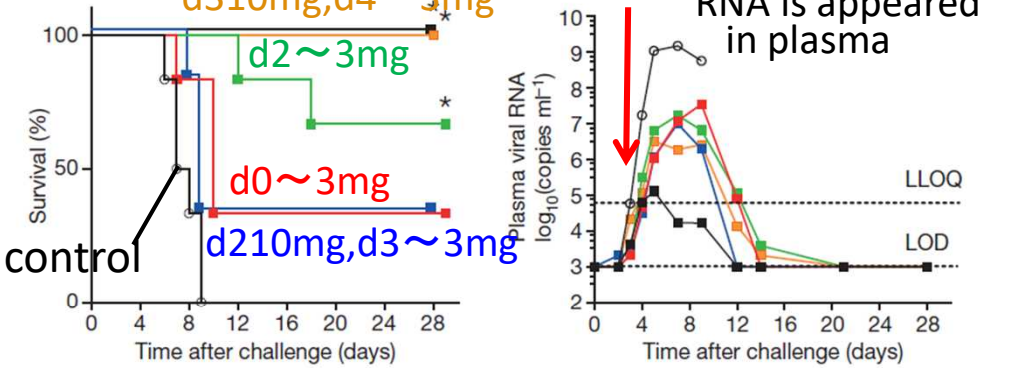


Figure 2 | GS-5734 pharmacokinetics and post-exposure protection against EBOV in rhesus monkeys. a, Pharmacokinetics following intravenous administration of 10 mg kg^{-1} GS-5734 dose in healthy rhesus macaques (mean ± s.d., $n = 3$). Plasma GS-5734 (black), alanine metabolite (red), and Nuc (blue); NTP in PBMCs (green). **b**, Tissue distribution of [^{14}C]GS-5734 and metabolites at 4 h (blue) and 168 h (red) following intravenous 10 mg kg^{-1} GS-5734 dose in healthy cynomolgus macaques (mean ± s.d., $n = 3$). **c**, Experimental design for GS-5734 efficacy evaluations in rhesus monkeys. No T_x, no treatment. **d**, Kaplan–Meier survival curves. *$P < 0.05$ for treatment versus vehicle groups assessed by log-rank analysis using Dunnett–Hsu procedure to adjust for multiple comparisons. **e**, Group geometric mean of plasma viral RNA concentrations; LLOQ, lower limit of quantitation; LOD, limit of detection. **f**, Individual plasma viral RNA in vehicle (blue) or 10 mg kg^{-1} GS-5734 (black) groups. **g**, Group average clinical disease score. **d**, **e**, **g**, Black (open symbols), vehicle; red, 3 mg kg^{-1} d0; green, 3 mg kg^{-1} d2; blue, 10/3 mg kg^{-1} d2; orange, 10/3 mg kg^{-1} d3; black (closed symbols), 10 mg kg^{-1} d3; $n = 6$ animals per group. Error bars omitted for clarity (**e**, **g**); x axes truncated to emphasize acute disease phase (**f**, **g**).

Animal experiment(2) : Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge

5) Lo MK et al. Sci Transl Med2019;11:eaau9242.

If remdesivir is administered one day after the inoculation and before the onset of symptoms, it reduced mortality. However no animal test was done in which remdesivir is administered after the onset of clinical symptoms.

Symptom onset in control group was d3

Remdesivir 24 hr after inoculation

All died within 8 days without remdesivir

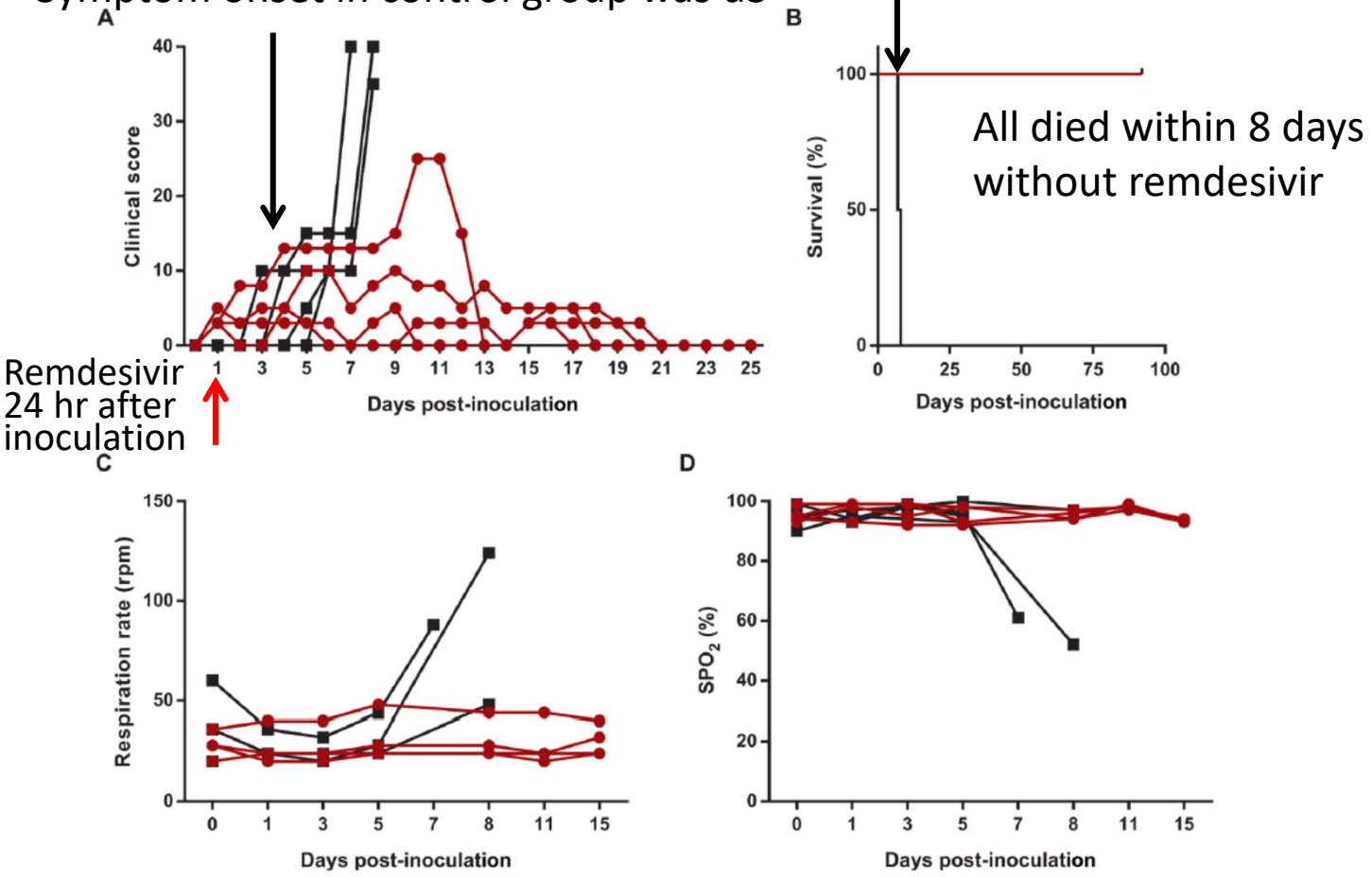


Fig. 1. Clinical signs in AGMs inoculated with a lethal dose of Nipah virus Bangladesh and treated with remdesivir. Two groups of four AGMs were inoculated intranasally and intratracheally with 10^5 $TCID_{50}$ of Nipah virus Bangladesh. At 1 dpi, the groups were treated intravenously with remdesivir (10 mg/kg, red circles) or vehicle solution (2 ml/kg, black squares); treatment was continued for 12 days. After inoculation, the animals were observed twice daily for clinical signs of disease and scored using a predetermined clinical scoring system (**A**). Survival after inoculation and treatment is indicated in (**B**). At regular time points after inoculation, clinical examinations were performed, during which respiration rate (**C**) and oxygen saturation (SPO_2) (**D**) were determined.

Animal experiment(3) : Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection

6) de Wit E et al. Proc Natl Acad Sci 2020;117:6771-6.

Prophylactic: remdesivir was started at one day before inoculation
Therapeutic: remdesivir was started at 12 hrs after inoculation

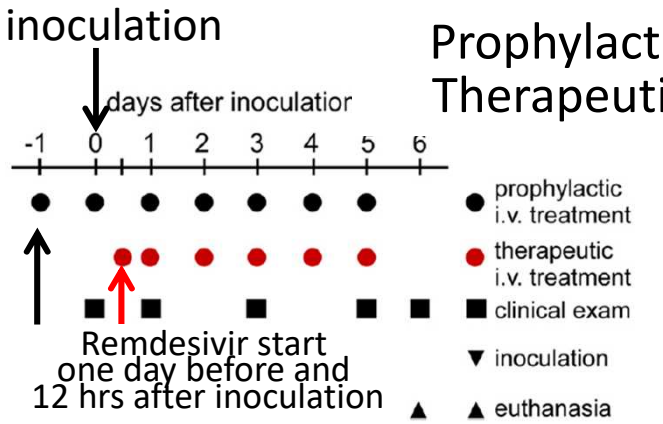
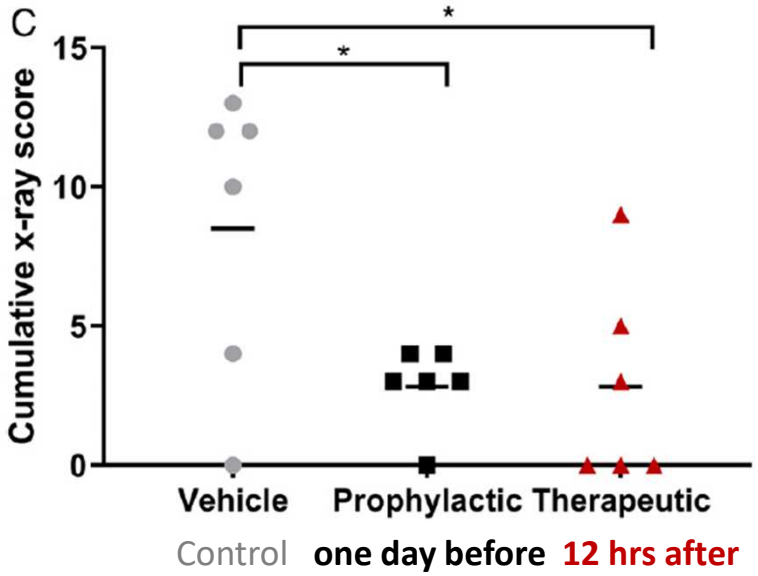
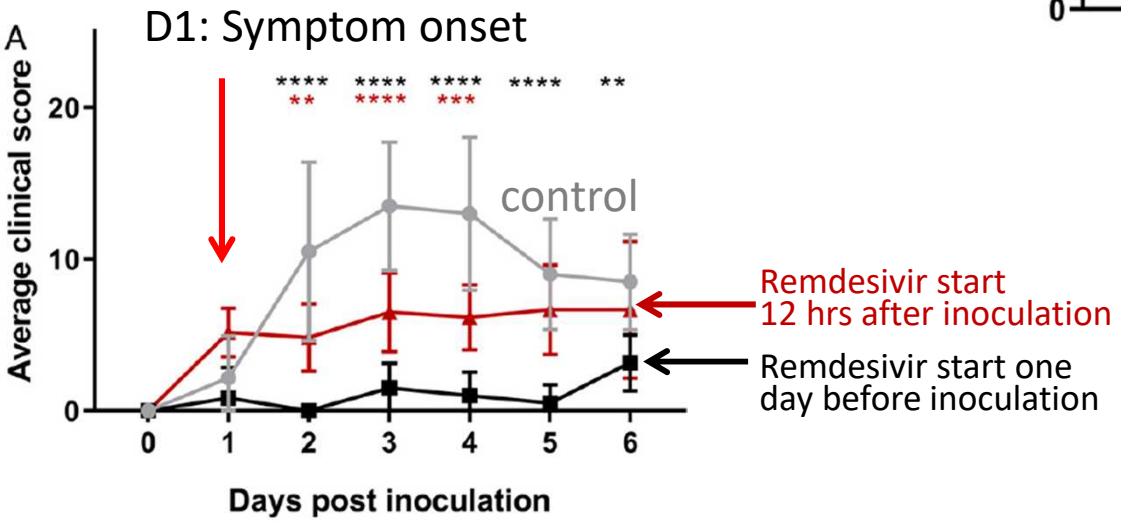


Fig. 1. Study outline. To test the prophylactic and therapeutic efficacy of remdesivir treatment in the rhesus macaque model of MERS-CoV infection, three groups of six rhesus macaques were inoculated with MERS-CoV strain HCoV-EMC/2012; one group was administered 5 mg/kg remdesivir starting at 24 h before inoculation (black circles), and one group was administered 5 mg/kg remdesivir starting at 12 h after inoculation (red circles). One group of six control animals was i.v.-administered 1 mL/kg vehicle solution, with three animals receiving vehicle solution according to the prophylactic treatment schedule, and three animals receiving it according to the therapeutic treatment schedule. Treatment was continued once daily until 6 dpi, when all animals were euthanized. At 0, 1, 3, 5, and 6 dpi, clinical examinations were performed to monitor the health status of the animals.





Animal experiment(4) : Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses

7) Sheahan TP et al. Transl Med. 2017:9(396):eaal3653.

Prophylactic: remdesivir was started at one day before inoculation
Therapeutic: remdesivir was started at one day after inoculation
No experiments was done in which remdesivir was commenced after onset of disease.

Symptom onset is at d2

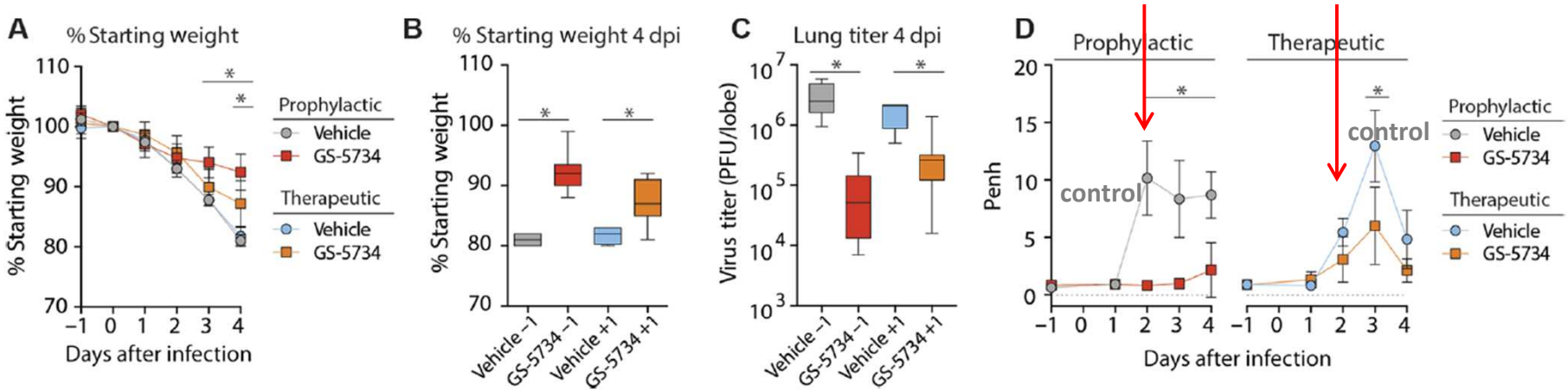


Fig. 6. Therapeutic postexposure administration of GS-5734 mitigates disease. (**A**) Percent starting weight of 27- to 28-week-old female *Ces1c*$^{-/-}$ mice infected with 10^3 PFU SARS-CoV MA15 and treated BID with vehicle or GS-5734 (25 mg/kg) beginning on either −1 dpi (vehicle, $n = 5$; GS-5734, $n = 10$) or +1 dpi (vehicle, $n = 4$; GS-5734, $n = 11$). Weights of GS-5734–treated animals were statistically different ($P < 0.05$) from those of vehicle-treated animals at 3 and 4 dpi for prophylactic groups and at 4 dpi for therapeutic groups by two-way ANOVA with Tukey's multiple comparison test. (**B**) Percent starting weights of mice in (A) at 4 dpi. (**C**) SARS-CoV lung titer in mice infected and treated as described in (A). Asterisks indicate statistical significance ($P < 0.05$) by Mann-Whitney test for (B) and (C). (**D**) WBP was used to measure the pulmonary function in mice infected and treated as described in (A). Penh is a surrogate measure of bronchoconstriction or airway obstruction. Asterisks indicate statistical significance by two-way ANOVA with Šidák's multiple comparison test.

WBP: whole-body plethysmography (pulmonary function test)

Mice were treated with 25mg/kg remdesivir b.i.d 50mg/kg/d⇒HED=4mg/kg/d (240mg/d for 60kg BW)

Animal experiment(5) : Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2

8) Williamson BN et al. bioRxiv 2020.04.15.043166. [Preprint.]

Therapeutic: This is rather prophylactic because administration started before onset of symptoms

Start 12hrs after

Figure legends

Symptom onset

Radiograph scores

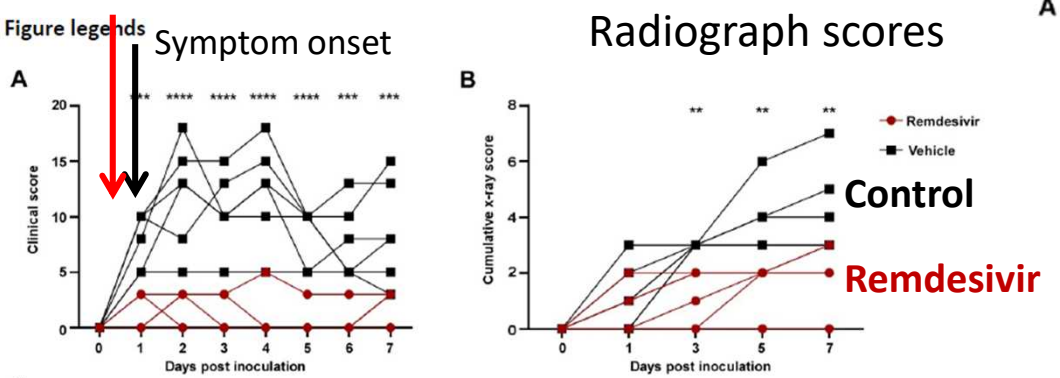


Figure 1. Reduced respiratory disease in rhesus macaques infected with SARS-CoV-2 and treated with remdesivir. Panel A shows daily clinical scores in animals infected with SARS-CoV-2 and treated with remdesivir (red circles) or vehicle solution (black squares). Panel B shows cumulative radiograph scores. Ventro-dorsal and lateral radiographs were scored for the presence of pulmonary infiltrates by a clinical veterinarian according to a standard scoring system (0: normal; 1: mild interstitial pulmonary infiltrates; 2: moderate pulmonary infiltrates perhaps with partial cardiac border effacement and small areas of pulmonary consolidation; 3: severe interstitial infiltrates, large areas of pulmonary consolidation, alveolar patterns and air bronchograms). Individual lobes were scored and scores per animal per day

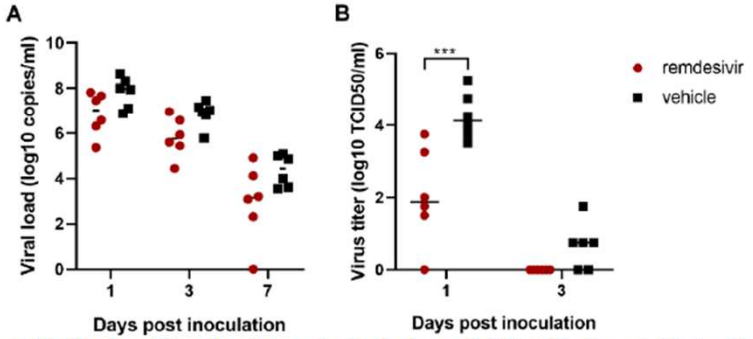
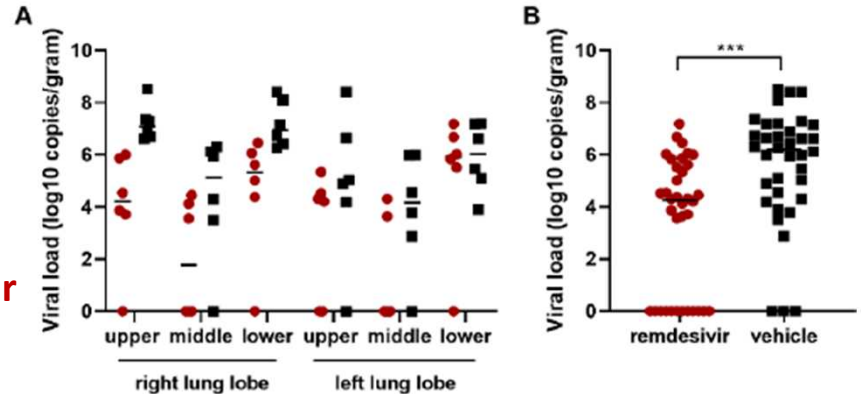


Figure 2. Viral loads and virus titers in bronchoalveolar lavage fluid. Panel A shows viral loads and Panel B shows infectious virus titers in BAL collected from rhesus macaques infected with SARS-CoV-2 and treated with remdesivir (red circles) or vehicle solution (black squares). Statistical analysis was performed using a 2-way ANOVA with Sidak's multiple comparisons test. *** P< 0.001



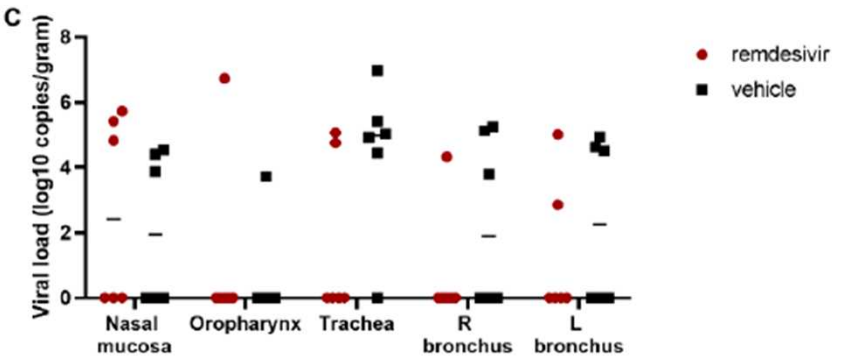


Figure 4. Viral loads in tissues collected from the respiratory tract on 7 dpi. Panel A shows viral loads in all six lung lobes collected from rhesus macaques infected with SARS-CoV-2 and treated with remdesivir (red circles) or vehicle solution (black squares), stratified per lung lobe. In panel B, all viral loads were combined. Statistical analysis was performed using an unpaired t test. ***P<0.001. Panel C shows viral loads in other tissues collected throughout the respiratory tract on 7 dpi.

These effects are not remarkable.

Remdesivir is not a remedy for Ebola virus infection (1)

A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics

9) Mulangu S et al. NEJM 2019: 381 (24): 2293-2303.

Remdesivir is the least effective among 4 agents including 3 monoclonal antibodies for reduction of mortality

Mortality 50% 53% 35% 34%

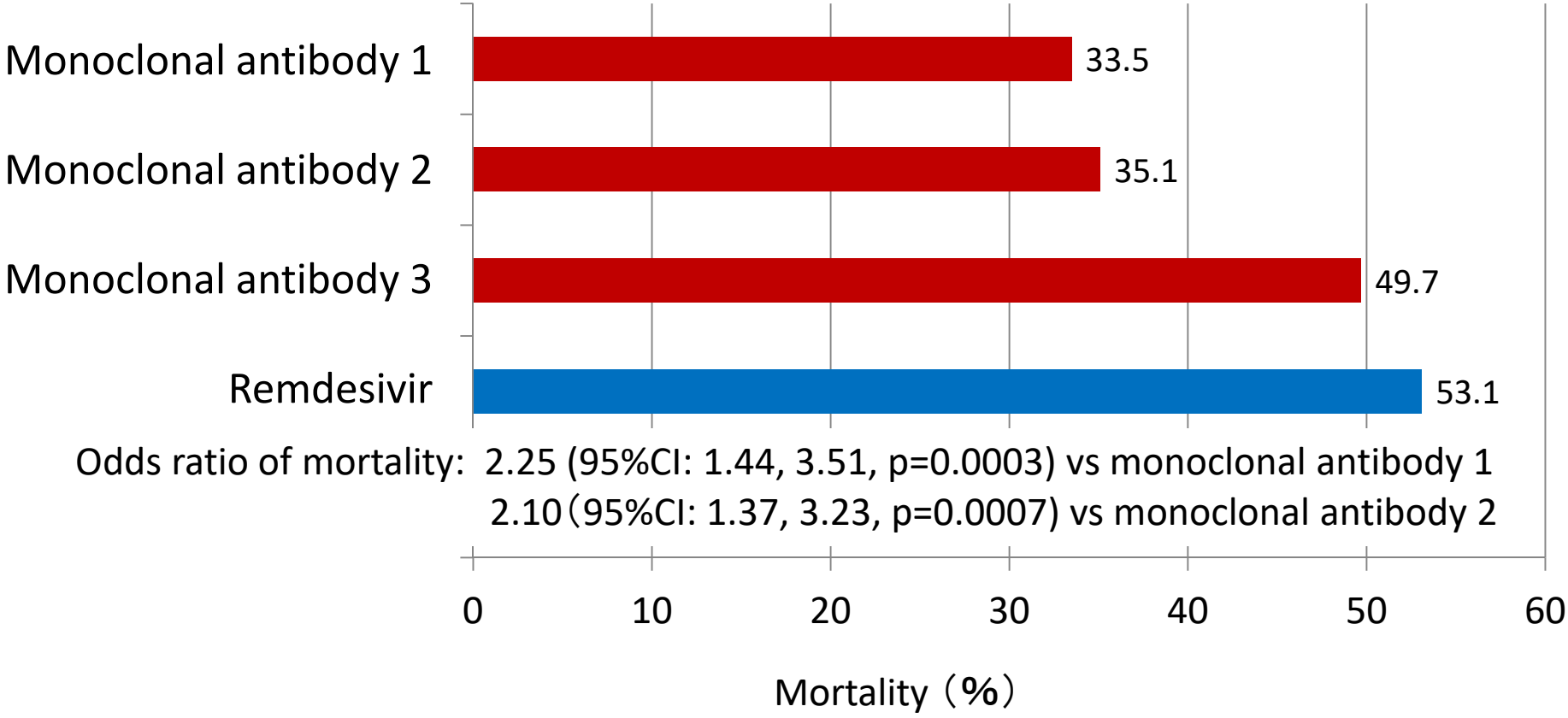
Table 2. Comparison of Death at 28 Days According to Treatment Group.

Population	ZMapp	Remdesivir	Difference, Remdesivir vs. ZMapp	MAb114	Difference, MAb114 vs. ZMapp	REGN-EB3	ZMapp Subgroup	Difference, REGN-EB3 vs. ZMapp Subgroup
	no. of deaths/ total no.(%)	*no. of deaths/ total no. (%)*	*percentage points (95% CI)*	*no. of deaths/ total no. (%)*	*percentage points (95% CI)*	*no. of deaths/ total no. (%)*	*no. of deaths/ total no. (%)*	*percentage points (95% CI)*
Overall	84/169 (49.7)	93/175 (53.1)	3.4 (−7.2 to 14.0)	61/174 (35.1)	−14.6 (−25.2 to −1.7)*	52/155 (33.5)	79/154 (51.3)	−17.8 (−28.9 to −2.9)*
Patients with high viral load†	60/71 (84.5)	64/75 (85.3)	0.8 (−15.3 to 17.2)	51/73 (69.9)	−14.6 (−33.0 to −0.5)	42/66 (63.6)	56/65 (86.2)	−22.5 (−41.8 to −5.1)
Patients with low viral load†	24/98 (24.5)	29/100 (29.0)	4.5 (−9.1 to 19.1)	10/101 (9.9)	−14.6 (−32.4 to −2.6)	10/89 (11.2)	23/89 (25.8)	−14.6 (−32.6 to −2.3)

* The result is significant according to the interim stopping boundary of P<0.035 for the MAb114 group and P<0.028 for the REGN-EB3 group.
† Patients with a high viral load had an EBOV nucleoprotein Ct value of 22.0 or less. Patients with a low viral load had an EBOV nucleoprotein Ct value of more than 22.0. The total number is the total number of patients in this category for each group.

Remdesivir is not a remedy for Ebola virus infection (2)

Less effective for reduction of mortality than any other monoclonal antibodies (more than doubled mortality)



Compared with 2 kinds of monoclonal antibody, remdesivir increases mortality by more than 2-fold from Ebola virus infection: **This indicates that Remdesivir is not a remedy for Ebola virus infection.**

Time course of special approval of Remdesivir

date	Source/facilities	contents
April 23	STAT (a news site in US)	Published screen shot of the summary of the Lancet [10] disclosed by WHO.
April 29	Wuhan RCT	Online publication at Lancet [10]: A placebo controlled RCT
April 29	NIH (US) Press release	Main results of ACTT [2] by National Institute of Allergy and Infectious Diseases (NIAID) : NCT04280705)
April 29	Gilead Sciences	Press release of SIMPLE trial
May 1	FDA (US)	EUA: Emergency Use Authorization
May 4	Gilead Sciences	Submitted approval application to MHLW
May 7	Japanese Advisory Panel for pharmaceuticals	Held by web-conference
May 7	Japanese MHLW	Special approval of remdesivir first in the wold
May 22	ACTT by NIAID	Online publication at NEJM [11] A placebo controlled RCT
May 27	SIMPLE trial	Online publication at NEJM [12] Comparison of 5 day- and 10 day-treatment

WuhanRCT(1)

10) Wang Y et al .Lancet. 2020: 395(10236): 1569-1578.

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang*

Summary

Background No specific antiviral drug has been proven effective for treatment of patients with severe coronavirus disease 2019 (COVID-19). Remdesivir (GS-5734), a nucleoside analogue prodrug, has inhibitory effects on pathogenic animal and human coronaviruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro, and inhibits Middle East respiratory syndrome coronavirus, SARS-CoV-1, and SARS-CoV-2 replication in animal models.

Methods We did a randomised, double-blind, placebo-controlled, multicentre trial at ten hospitals in Hubei, China. Eligible patients were adults (aged ≥18 years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, with an interval from symptom onset to enrolment of 12 days or less, oxygen saturation of 94% or less on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and radiologically confirmed pneumonia. Patients were randomly assigned in a 2:1 ratio to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for 10 days. Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids. The primary endpoint was time to clinical improvement up to day 28, defined as the time (in days) from randomisation to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1=discharged to 6=death) or discharged alive from hospital, whichever came first. Primary analysis was done in the intention-to-treat (ITT) population and safety analysis was done in all patients who started their assigned treatment. This trial is registered with ClinicalTrials.gov, NCT04257656.

Findings Between Feb 6, 2020, and March 12, 2020, 237 patients were enrolled and randomly assigned to a treatment group (158 to remdesivir and 79 to placebo); one patient in the placebo group who withdrew after randomisation was not included in the ITT population. Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio 1·52 [0·95–2·43]). Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early.

Interpretation In this study of adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies.

Funding Chinese Academy of Medical Sciences Emergency Project of COVID-19, National Key Research and Development Program of China, the Beijing Science and Technology Project.

Wuhan RCT(2): Main baseline characteristics

No difference

	Remdesivir group (n=158)	Placebo group (n=78)
National Early Warning Score 2 level at day 1	5·0 (3·0–7·0)	4·0 (3·0–6·0)
Six-category scale at day 1		
2—hospital admission, not requiring supplemental oxygen	0	3 (4%)
3—hospital admission, requiring supplemental oxygen	129 (82%)	65 (83%)
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	28 (18%)	9 (12%)
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	0	1 (1%)
6—death	1 (1%)	0
Baseline viral load of nasopharyngeal and oropharyngeal swabs, log_{10} copies per mL	4·7 (0·3)	4·7 (0·4)
Receiving interferon alfa-2b at baseline	29 (18%)	15 (19%)
Receiving lopinavir–ritonavir at baseline	27 (17%)	15 (19%)
Antibiotic treatment at baseline	121 (77%)	63 (81%)
Corticosteroids therapy at baseline	60 (38%)	31 (40%)

Data are median (IQR), n (%), n/N (%), or mean (SE).

Table 1: **Baseline patient characteristics**

Wuhan RCT(3) Different baseline characteristics

	Remdesivir group (n=158)		Placebo group (n=78)	
Time from symptom onset to starting study treatment, days*	11 (9–12)		10 (9–12)	
Early (≤10 days from symptom onset)	71/155 (46%)	<	47 (60%)	P=0.037
Late (>10 days from symptom onset)	84/155 (54%)	>	31 (40%)	
Receiving injection of interferon alfa-2b	46 (29%)		30 (38%)	
Receiving lopinavir–ritonavir	44 (28%)		23 (29%)	
Vasopressors	25 (16%)		13 (17%)	
Renal replacement therapy	3 (2%)		3 (4%)	
Highest oxygen therapy support				
Non-invasive mechanical ventilation	14 (9%)		3 (4%)	
Invasive mechanical ventilation	11 (7%)		10 (13%)	
Extracorporeal membrane oxygenation or mechanical ventilation	2 (1%)		0	
Antibiotic	142 (90%)		73 (94%)	
Corticosteroids therapy	102 (65%)		53 (68%)	
Time from symptom onset to corticosteroids therapy, days	9 (7–11)		8 (6–10)	
Duration of corticosteroids therapy, days	9 (5–15)		10 (6–16)	

Data are median (IQR) or n (%). *Three patients did not start treatment so are not included in time from symptom onset to start of study treatment subgroup analyses.

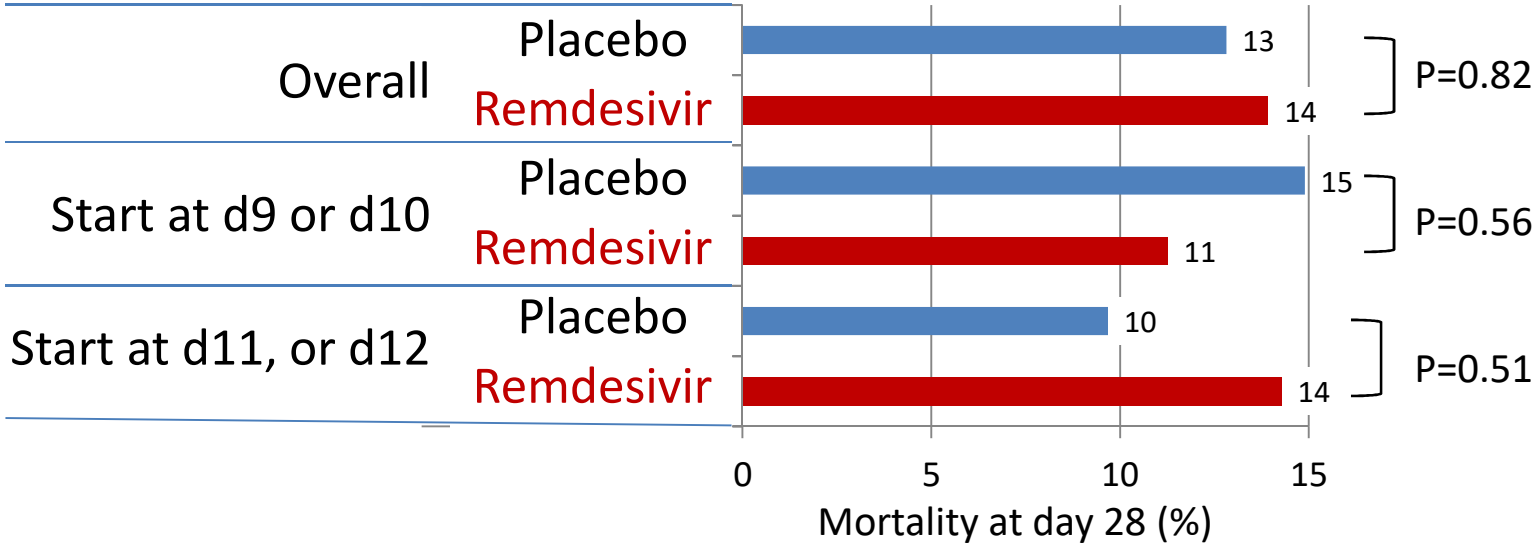
Others are not different

Table 2: **Treatments received before and after enrolment**

Wuhan RCT(4) Day 28 mortality by early or late commencement of remdesivir

	Remdesivir group (n=158)	Placebo group (n=78)	Difference*
Time to clinical improvement	21·0 (13·0 to 28·0)	23·0 (15·0 to 28·0)	1·23 (0·87 to 1·75)†
Day 28 mortality	22 (14%)	10 (13%)	1·1% (−8·1 to 10·3)
Early (≤10 days of symptom onset)	8/71 (11%)	7/47 (15%)	−3·6% (−16·2 to 8·9)
Late (>10 days of symptom onset)	12/84 (14%)	3/31 (10%)	4·6% (−8·2 to 17·4)
Clinical improvement rates			
Day 7	4 (3%)	2 (3%)	0·0% (−4·3 to 4·2)
Day 14	42 (27%)	18 (23%)	3·5% (−8·1 to 15·1)
Day 28	103 (65%)	45 (58%)	7·5% (−5·7 to 20·7)
Duration of invasive mechanical ventilation, days	7·0 (4·0 to 16·0)	15·5 (6·0 to 21·0)	−4·0 (−14·0 to 2·0)
Duration of invasive mechanical ventilation in survivors, days‡	19·0 (5·0 to 42·0)	42·0 (17·0 to 46·0)	−12·0 (−41·0 to 25·0)
Duration of invasive mechanical ventilation in non-survivors, days‡	7·0 (2·0 to 11·0)	8·0 (5·0 to 16·0)	−2·5 (−11·0 to 3·0)
Duration of oxygen support, days	19·0 (11·0 to 30·0)	21·0 (14·0 to 30·5)	−2·0 (−6·0 to 1·0)
Duration of hospital stay, days	25·0 (16·0 to 38·0)	24·0 (18·0 to 36·0)	0·0 (−4·0 to 4·0)
Time from random group assignment to discharge, days	21·0 (12·0 to 31·0)	21·0 (13·5 to 28·5)	0·0 (−3·0 to 3·0)
Time from random group assignment to death, days	9·5 (6·0 to 18·5)	11·0 (7·0 to 18·0)	−1·0 (−7·0 to 5·0)

Mortality at d28
d9, d10
d11, d12



Wuhan RCT (5)：Kaplan-Meier curve of clinical improvement(ITT）

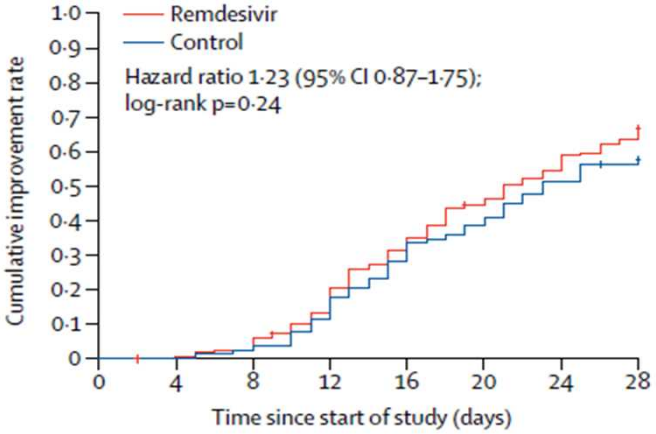
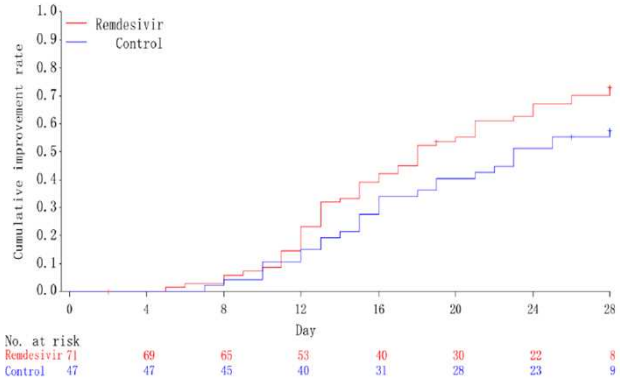
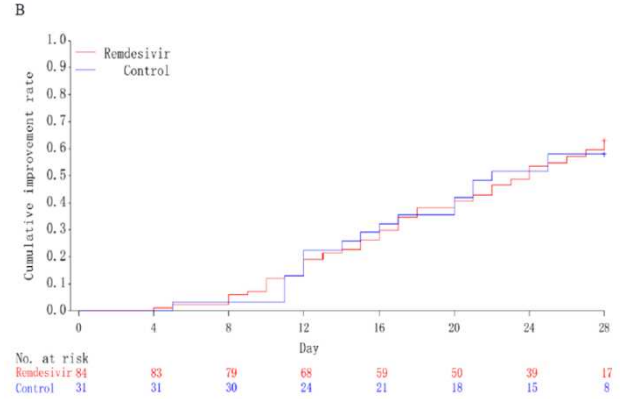


Figure 2: **Time to clinical improvement in the intention-to-treat Population:** Adjusted hazard ratio for randomisation stratification was 1·25 (95% CI: 0·88–1·78). *Including deaths before day 28 as right censored at day 28, the number of patients without clinical improvement was still included in the number at risk.



(A) Start early (at d9 or d10)
median days to clinical improvement
18 days vs 23 days

Hazard ratio: 1.52; 95%CI：0.95 - 2.43



(B) Start late (at d11 or d12)(B)
median days to clinical improvement
23 days vs 24 days

Hazard ratio: 1.07; 95% CI, 0.63 - 1.83

Wuhan RCT(6): Adverse Events (AEs)

	Remdesivir group (n=155)		Placebo group (n=78)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Adverse events (in ≥2% of patients in any treatment group)				
Any	102 (66%)	13 (8%)	50 (64%)	11 (14%)
Hypoalbuminaemia	20 (13%)	0	12 (15%)	1 (1%)
Hypokalaemia	18 (12%)	2 (1%)	11 (14%)	1 (1%)
Increased blood glucose	11 (7%)	0	6 (8%)	0
Anaemia	18 (12%)	1 (1%)	12 (15%)	2 (3%)
Rash	11 (7%)	0	2 (3%)	0
Thrombocytopenia	16 (10%)	4 (3%)	5 (6%)	3 (4%)
Increased total bilirubin	15 (10%)	1 (1%)	7 (9%)	0
Increased blood lipids	10 (6%)	0	8 (10%)	0
Increased white blood cell count	11 (7%)	0	6 (8%)	0
Hyperlipidaemia	10 (6%)	0	8 (10%)	0
Increased blood urea nitrogen	10 (6%)	0	5 (6%)	0
Increased neutrophil	10 (6%)	0	4 (5%)	0
Aspartate aminotransferase increased	7 (5%)	0	9 (12%)	0
Constipation	21 (14%)	0	12 (15%)	0
Nausea	8 (5%)	0	2 (3%)	0
Diarrhoea	5 (3%)	0	2 (3%)	0
Vomiting	4 (3%)	0	2 (3%)	0
Reduced serum sodium	4 (3%)	0	2 (3%)	0
Increased serum potassium	4 (3%)	2 (1%)	1 (1%)	0

Most serious adverse events were not different

Serious Adverse Events

	Remdesivir group (n=155)		Placebo group (n=78)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Serious adverse events				
Any	28 (18%)	9 (6%)	20 (26%)	10 (13%)
Respiratory failure or acute respiratory distress syndrome	16 (10%)	4 (3%)	6 (8%)	4 (5%)
Cardiopulmonary failure	8 (5%)	0	7 (9%)	1 (1%)
Pulmonary embolism	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Recurrence of COVID-19	1 (1%)	0	0	0
Cardiac arrest	1 (1%)	0	0	0
Acute coronary syndrome	0	0	1 (1%)	1 (1%)
Tachycardia	0	0	1 (1%)	0
Septic shock	1 (1%)	0	1 (1%)	1 (1%)
Lung abscess	0	0	1 (1%)	1 (1%)
Sepsis	0	0	1 (1%)	1 (1%)
Bronchitis	0	0	1 (1%)	1 (1%)
Thrombocytopenia	1 (1%)	1 (1%)	0	0
Increased D-dimer	0	0	1 (1%)	1 (1%)
Haemorrhage of lower digestive tract	1 (1%)	1 (1%)	0	0
Ileus	0	0	1 (1%)	0
Deep vein thrombosis	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Acute kidney injury	1 (1%)	0	0	0
Diabetic ketoacidosis	0	0	1 (1%)	1 (1%)
Multiple organ dysfunction syndrome	1 (1%)	0	2 (3%)	0

Wuhan RCT(7): Events leading to discontinuation

	Remdesivir group (n=155)		Placebo group (n=78)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Events leading to drug discontinuation				
Any	18 (12%)	3 (2%)	4 (5%)	1 (1%)
Respiratory failure or acute respiratory distress syndrome	7 (5%)	1 (1%)	1 (1%)	0
Secondary infection	4 (3%)	0	7 (9%)	2 (3%)
Cardiopulmonary failure	3 (2%)	0	1 (1%)	0
Nausea	1 (1%)	0	0	0
Vomiting	1 (1%)	0	0	0
Ileus	0	0	1 (1%)	0
Increased alanine aminotransferase	2 (1%)	1 (1%)	0	0
Rash	2 (1%)	0	0	0
Poor appetite	1 (1%)	0	0	0
Increased total bilirubin	1 (1%)	0	0	0
Acute kidney injury	1 (1%)	1 (1%)	0	0
Seizure	0	0	1 (1%)	0
Aggravated schizophrenia	0	0	1 (1%)	1 (1%)
Aggravated depression	0	0	1 (1%)	1 (1%)

Respiratory failure/ARDS: p=0.20

Serious Adverse Events

	Remdesivir group (n=155)		Placebo group (n=78)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Serious adverse events				
Any	28 (18%)	9 (6%)	20 (26%)	10 (13%)
Respiratory failure or acute respiratory distress syndrome	16 (10%)	4 (3%)	6 (8%)	4 (5%)
Cardiopulmonary failure	8 (5%)	0	7 (9%)	1 (1%)
Pulmonary embolism	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Recurrence of COVID-19	1 (1%)	0	0	0
Cardiac arrest	1 (1%)	0	0	0
Acute coronary syndrome	0	0	1 (1%)	1 (1%)
Tachycardia	0	0	1 (1%)	0
Septic shock	1 (1%)	0	1 (1%)	1 (1%)

(Table 4 continues in next column)

Non-significant increase of respiratory failure/ARDS leading to discontinuation was observed in Remdesivir group. Respiratory failure and ARDS are main symptoms of COVID-19.

What does this mean?

Wuhan RCT(8) : Accumulated rate of undetectable viral RNA in upper respiratory tract specimen in viral positive population

Viral load

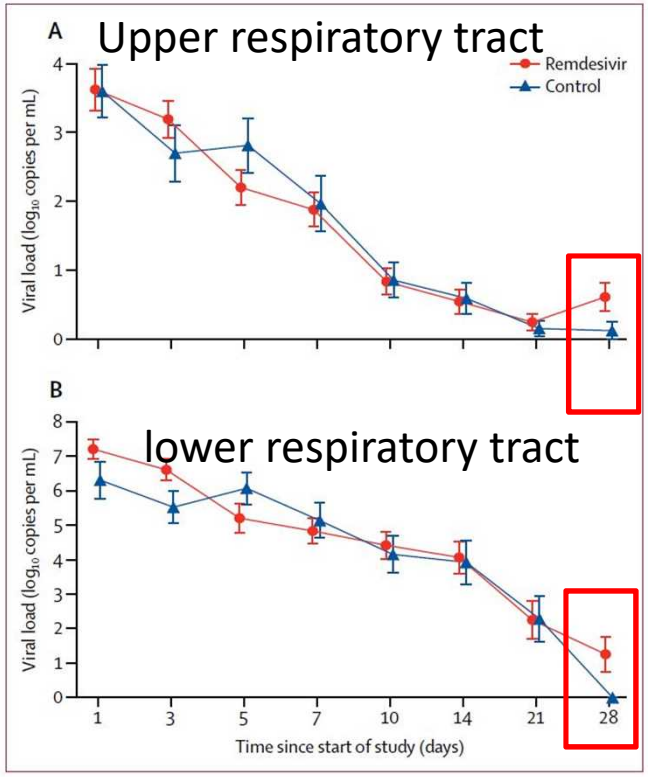


Figure 3: **Viral load by quantitative PCR on the upper respiratory tract specimens (A) and lower respiratory tract specimens (B)**
Data are mean (SE). Results less than the lower limit of quantification of the PCR assay and greater than the limit of qualitative detection are imputed with half of actual value; results of patients with viral-negative RNA are imputed with 0 log_{10} copies per mL.

Undetectable viral RNA in Remdesivir group was nearly 10 % lower than control group especially in the survivours. What does this mean?

Table S2. Accumulated rate of undetectable viral RNA in upper respiratory tract specimens in viral positive population.

Study day	Total (n = 196)	Remdesivir group (n = 131)	Control group (n = 65)	Difference§
Baseline	37/196 (18.9%)	24/131 (18.3%)	13/65 (20.0%)	-1.7 (-13.4 to 10.1)
Day 3, n (%)	56/196 (28.6%)	37/131 (28.2%)	19/65 (29.2%)	-1.0 (-14.5 to 12.5)
Day 5	78/196 (39.8%)	53/131 (40.5%)	25/65 (38.5%)	2.0 (-12.5 to 16.5)
Day 7	98/196 (50.0%)	66/131 (50.4%)	32/65 (49.2%)	1.2 (-13.7 to 16.0)
Day 10	127/196 (64.8%)	82/131 (62.6%)	45/65 (69.2%)	-6.6 (-20.6 to 7.3)
Day 14	142/196 (72.4%)	93/131 (71.0%)	49/65 (75.4%)	-4.4 (-17.4 to 8.6)
Day 21	151/196 (77.0%)	98/131 (74.8%)	53/65 (81.5%)	-6.7 (-18.7 to 5.3)
Day 28	153/196 (78.1%)	99/131 (75.6%)	54/65 (83.1%)	-7.5 (-19.2 to 4.2)
Survivors, n	167	112	55	
Baseline	33/167 (19.8%)	21/112 (18.8%)	12/55 (21.8%)	-3.1 (-16.2 to 10.0)
Day 3, n (%)	49/167 (29.3%)	32/112 (28.6%)	17/55 (30.9%)	-2.3 (-17.1 to 12.5)
Day 5	70/167 (41.9%)	47/112 (42.0%)	23/55 (41.8%)	0.1 (-15.8 to 16.1)
Day 7	89/167 (53.3%)	59/112 (52.7%)	30/55 (54.5%)	-1.9 (-18.0 to 14.2)
Day 10	117/167 (70.1%)	75/112 (67.0%)	42/55 (76.4%)	-9.4 (-23.6 to 4.8)
Day 14	131/167 (78.4%)	85/112 (75.9%)	46/55 (83.6%)	-7.7 (-20.3 to 4.8)
Day 21	138/167 (82.6%)	89/112 (79.5%)	49/55 (89.1%)	-9.6 (-20.8 to 1.5)
Day 28	139/167 (83.2%)	90/112 (80.4%)	49/55 (89.1%)	-8.7 (-19.8 to 2.3)
Non-survivors, n*	29	19	10	
Baseline	4/29 (13.8%)	3/19 (15.8%)	1/10 (10.0%)	5.8 (-19.0 to 30.6)
Day 3, n (%)	7/29 (24.1%)	5/19 (26.3%)	2/10 (20.0%)	6.3 (-25.4 to 38.0)
Day 5	8/29 (27.6%)	6/19 (31.6%)	2/10 (20.0%)	11.6 (-20.8 to 44.0)
Day 7	9/29 (31.0%)	7/19 (36.8%)	2/10 (20.0%)	16.8 (-16.1 to 49.8)
Day 10	10/29 (34.5%)	7/19 (36.8%)	3/10 (30.0%)	6.8 (-28.9 to 42.6)
Day 14	11/29 (37.9%)	8/19 (42.1%)	3/10 (30.0%)	12.1 (-23.9 to 48.2)
Day 21	13/29 (44.8%)	9/19 (47.4%)	4/10 (40.0%)	7.4 (-30.4 to 45.1)
Day 28	14/29 (48.3%)	9/19 (47.4%)	5/10 (50.0%)	-2.6 (-40.9 to 35.6)

* Totally, 35 patients died during the hospitalization, otherwise there were 32 fatal cases until day 28; Respiratory specimens of 27 patients in remdesivir group and 13 patients in control group were not collected because safety of medical care workers during aerosol generating procedures cannot be guaranteed in one study site

ACTT trial（1）

Remdesivir for the Treatment of Covid-19 — Preliminary Report

11) Beigel JH et al. NEJM. 2020 May 22.

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 infectioncontrol 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; ACCT-1 ClinicalTrials.gov number, NCT04280705.)

Adjusted HR for death= 0.74(95%CI：0.50 to 1.10)

ACTT trial（2）Baseline characteristics

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.

Level 7:
Receiving invasive mechanical ventilation or ECMO

23% vs 28%

P=0.059

ACTT trial（**3**） Fig. 2　Kaplan-Meier estimates of cumulative recoveries by baseline severity.

Level 4．Not receiving oxygen

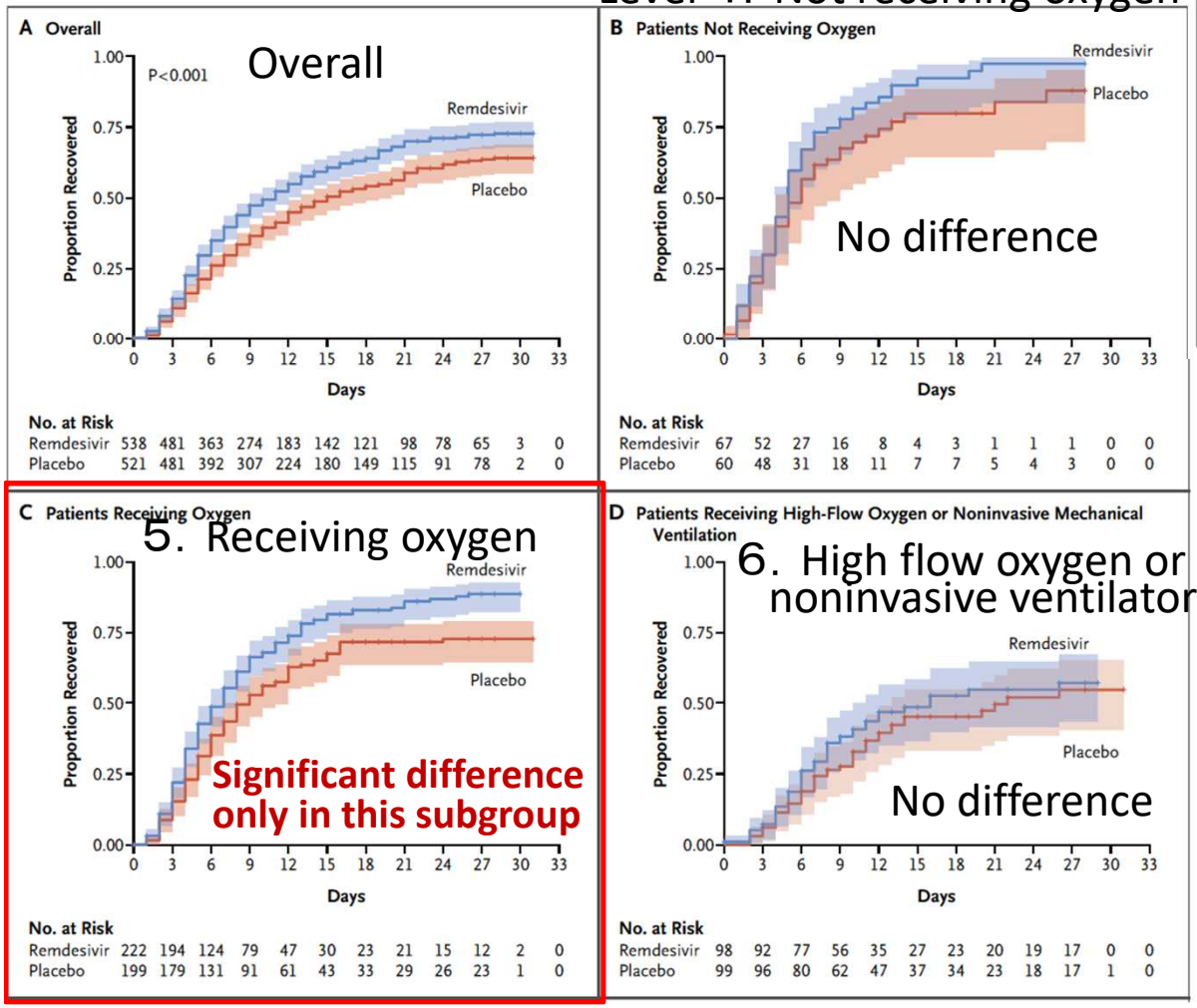
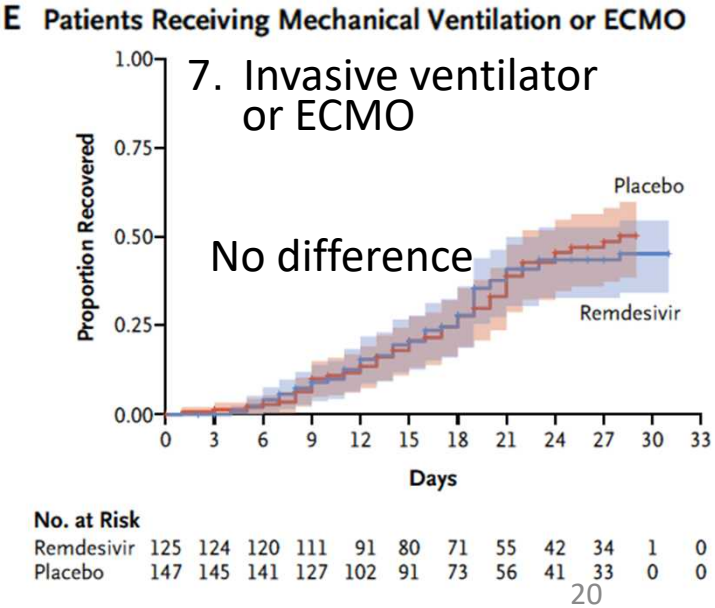


Figure 2 (facing page). Kaplan–Meier Estimates of Cumulative Recoveries.

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).



ACTT trial (4)

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

	Overall*		Ordinal Score at Baseline							
			4. No O_2		5. O_2		6.High O_2		7. Invasive MV/ECMO	
	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. (%)‡					2.9% vs 11%					
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)	

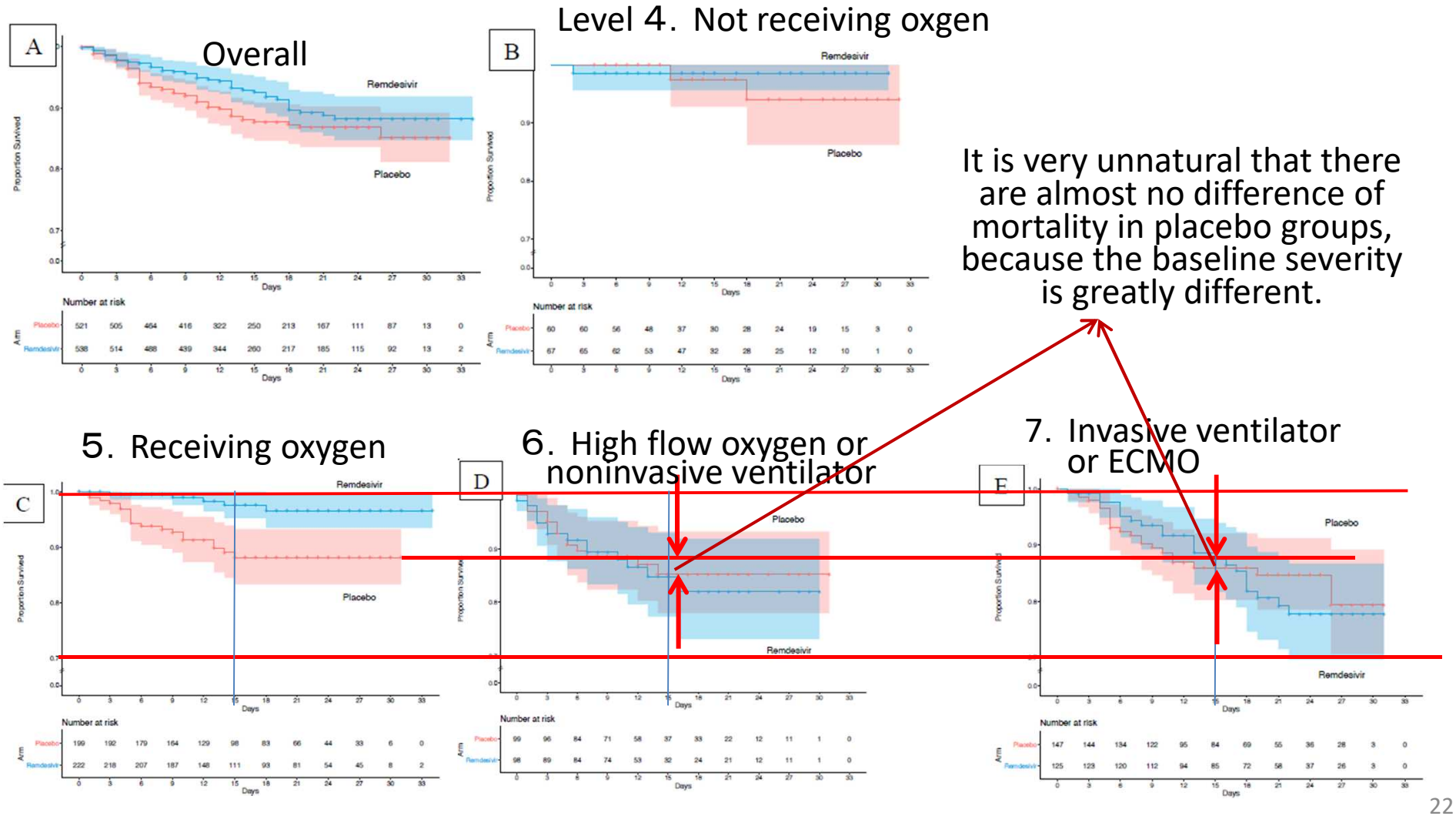
* P values and confidence intervals have not been adjusted for multiple comparisons. NE denotes not possible to estimate.

† 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.

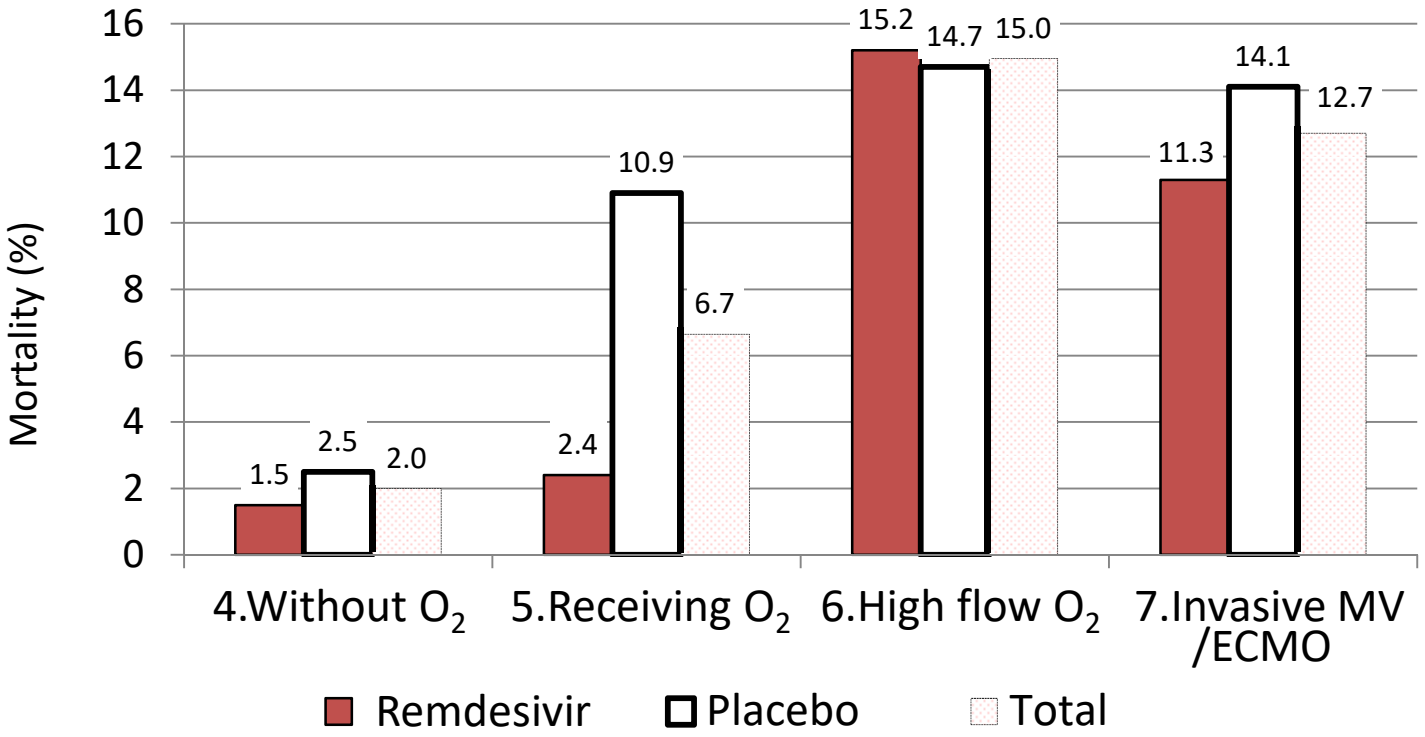
ACTT trial（5） Kaplan-Meier Estimate of Survival by baseline

Figure S3. Kaplan–Meier Estimates of Survival by Baseline Ordinal Scale.
Panel A shows the estimates (and 95% confidence bands) in the overall population, Panel B in those with baseline ordinal scale = 4, Panel C in those with baseline ordinal scale = 5, Panel D in those with baseline ordinal scale = 6, and Panel E in those with baseline ordinal scale = 7.



Unnatural: mortality of placebo group is not different between subgroup 5 and more severe subgroup 6/7

ACTT trial（6）：Comparison of day 14 mortality by baseline severity （Kaplan-Meier estimate ）



In all subgroups by baseline severity except level 5, mortality risk was not different between Remdesivir arm ■ and placebo group □. Only in the subgroup of level 5 (receiving O_2) mortality was extremely different. But in the subgroup of level 5, mortality of placebo group is unnaturally high (almost the same as those of the subgroups 6 or 7 with greater baseline severity) and mortality of remdesivir group is unnaturally low (almost the same as that of the subgroup 4). It is very hard to find appropriate reasons why Remdesivir was effective only in the level 5.

ACTT trial（7）Summary: Critical appraisal of preliminary report

1. There was no significant difference between remdesivir arm and placebo arm except one, proportion of the level 7 of the baseline severity which was non-significantly different (p=0.059).

2. Comparing the improvement of clinical symptoms and the overall survival by baseline severity, there was no difference between both groups in the sub groups of levels 4, 6 and 7. Difference was only observed in the subgroup of level 5 (receiving oxygen).

3. At the level 5, all-cause mortality of the placebo group was unnaturally high, and there was no significant difference from that at the levels 6 and 7.

4. On the other hand, all-cause mortality of the Remdesivir group in the level 5 was unnaturally low, and there was almost no difference from that at the level 4.

5. If Remdesivir group and placebo group of the subgroup level 5 were combined, all-cause mortality of the level 5 was at the mid point between levels 4 and 6 or 7 and this is very natural biologically.

6. Taken together, it is doubtful whether 421 patients in the subgroup of level 5 was appropriately allocated at randomization.

7. Unless details of baseline characteristics of the Level 5 subgroup (222 patients in the remdesivir group and 199 patients in the placebo group) are available and it is confirmed that there is no difference in the baseline characteristics, the results of this study remains unreliable. The baseline characteristics include distribution of oxygen partial pressure or oxygen saturation, distribution of laboratory data related to severity, such as creatinine level and severity score such as APACHE II, MEDS, SAPS II or SOFA.

APACHE II = Acute Physiology and Chronic Health Evaluation II, MEDS = Mortality in Emergency Department Sepsis Score, SAPS II = New Simplified Acute Physiology Score, SOFA = Sequential Organ Failure Assessment.

SIMPLE trial（1）

ORIGINAL ARTICLE

Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

for the GS-US-540-5773 Investigators*

13)Goldman JD et al NEJM 2020 May 27

BACKGROUND

Remdesivir is an RNA polymerase inhibitor with potent antiviral activity in vitro and efficacy in animal models of coronavirus disease 2019 (Covid-19).

METHODS

We conducted a randomized, open-label, phase 3 trial involving hospitalized patients with confirmed SARS-CoV-2 infection, oxygen saturation of 94% or less while they were breathing ambient air, and radiologic evidence of pneumonia. Patients were randomly assigned in a 1:1 ratio to receive intravenous remdesivir for either 5 days or 10 days. All patients received 200 mg of remdesivir on day 1 and 100 mg once daily on subsequent days. The primary end point was clinical status on day 14, assessed on a 7-point ordinal scale.

RESULTS

In total, 397 patients underwent randomization and began treatment (200 patients for 5 days and 197 for 10 days). The median duration of treatment was 5 days (interquartile range, 5 to 5) in the 5-day group and 9 days (interquartile range, 5 to 10) in the 10-day group. At baseline, patients randomly assigned to the 10-day group had significantly worse clinical status than those assigned to the 5-day group (P=0.02). By day 14, a clinical improvement of 2 points or more on the ordinal scale occurred in 64% of patients in the 5-day group and in 54% in the 10-day group. After adjustment for baseline clinical status, patients in the 10-day group had a distribution in clinical status at day 14 that was similar to that among patients in the 5-day group (P=0.14). The most common adverse events were nausea (9% of patients), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%).

CONCLUSIONS

In patients with severe Covid-19 not requiring mechanical ventilation, our trial did not show a significant difference between a 5-day course and a 10-day course of remdesivir. With no placebo control, however, the magnitude of benefit cannot be determined. (Funded by Gilead Sciences; GS-US-540-5773 ClinicalTrials.gov number, NCT04292899.)

SIMPLE trial（2）

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline According to Remdesivir Treatment Group.*

Characteristic	5-Day Group (N=200)	10-Day Group (N=197)
Median age (IQR) — yr	61 (50–69)	62 (50–71)
Male sex — no. (%)	120 (60)	133 (68)
Race — no./total no. (%)†		
White	142/200 (71)	134/192 (70)
Black	21/200 (10)	23/192 (12)
Asian	20/200 (10)	25/192 (13)
Other	17/200 (8)	10/192 (5)
Median body-mass index (IQR)‡	29 (25–34)	29 (25–33)
Coexisting conditions of interest — no. (%)		
Diabetes	47 (24)	43 (22)
Hyperlipidemia	40 (20)	49 (25)
Hypertension	100 (50)	98 (50)
Asthma	27 (14)	22 (11)
Clinical status on the 7-point ordinal scale — no. (%)§		
2: Receiving invasive mechanical ventilation or ECMO	4 (2)	9 (5)
3: Receiving noninvasive ventilation or high-flow oxygen	49 (24)	60 (30)
4: Receiving low-flow supplemental oxygen	113 (56)	107 (54)
5: Not receiving supplemental oxygen but requiring medical care	34 (17)	21 (11)
Median duration of hospitalization before first dose of remdesivir (IQR) — days	2 (1–3)	2 (1–3)
Median duration of symptoms before first dose of remdesivir (IQR) — days	8 (5–11)	9 (6–12)
Median AST level (IQR) — U/liter¶	41 (29–58)	46 (34–67)
Median ALT level (IQR) — U/liter	32 (22–50)	36 (23–58)
Median creatinine clearance by Cockcroft–Gault (IQR) — ml/min	106 (80–142)	103 (80–140)

* Percentages may not total 100 because of rounding. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and IQR interquartile range.
† Race was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ P=0.02 for the comparison between the 5-day group and the 10-day group by the Wilcoxon rank-sum test.
¶ P=0.008 for the comparison between the 5-day group and the 10-day group by the Wilcoxon rank-sum test.

SIMPLE trial（3）Results

Table 2. Clinical Outcomes According to Remdesivir Treatment Group.

Characteristic	5-Day Group (N=200)	10-Day Group (N=197)	Baseline-Adjusted Difference (95% CI)*
Clinical status at day 14 on the 7-point ordinal scale — no. of patients (%)			P=0.14†
1: Death	16 (8)	21 (11)	
2: Hospitalized, receiving invasive mechanical ventilation or ECMO	16 (8)	33 (17)	
3: Hospitalized, receiving noninvasive ventilation or high-flow oxygen	9 (4)	10 (5)	
4: Hospitalized, requiring low-flow supplemental oxygen	19 (10)	14 (7)	
5: Hospitalized, not receiving supplemental oxygen but requiring ongoing medical care	11 (6)	13 (7)	
6: Hospitalized, not requiring supplemental oxygen or ongoing medical care	9 (4)	3 (2)	
7. Not hospitalized	120 (60)	103 (52)	
Time to clinical improvement (median day of 50% cumulative incidence‡)	10	11	0.79 (0.61 to 1.01)
Clinical improvement — no. of patients (%)			
Day 5	33 (16)	29 (15)	0.2% (–7.0 to 7.5)
Day 7	71 (36)	54 (27)	–5.0% (–14.0 to 4.0)
Day 11	116 (58)	97 (49)	–4.8% (–14.1 to 4.6)
Day 14	129 (64)	107 (54)	–6.5% (–15.7 to 2.8)
Time to recovery (median day of 50% cumulative incidence‡)	10	11	0.81 (0.64 to 1.04)
Recovery — no. of patients (%)			
Day 5	32 (16)	27 (14)	0.1% (–7.0 to 7.1)
Day 7	71 (36)	51 (26)	–6.0% (–14.8 to 2.7)
Day 11	115 (58)	97 (49)	–3.7% (–12.8 to 5.5)
Day 14	129 (64)	106 (54)	–6.3% (–15.4 to 2.8)
Time to modified recovery (median day of 50% cumulative incidence‡)	9	10	0.82 (0.64 to 1.04)
Modified recovery — no. of patients (%)			
Day 5	51 (26)	41 (21)	–2.3% (–10.5 to 5.9)
Day 7	84 (42)	69 (35)	–3.4% (–12.6 to 5.8)
Day 11	128 (64)	106 (54)	–5.7% (–14.6 to 3.2)
Day 14	140 (70)	116 (59)	–6.7% (–15.3 to 1.9)

* Differences are expressed as rate differences, except in the case of time to clinical improvement, time to recovery, and time to modified recovery, for which differences are expressed as hazard ratios; for these time-to-event end points, the hazard ratio and its 95% confidence interval were estimated from a cause-specific proportional-hazards model including treatment and baseline clinical status as covariates. For events at prespecified time points (e.g., days 5, 7, 11, and 14), the difference in the proportion of subjects with an event under evaluation between treatment groups and the 95% confidence interval were estimated from the Mantel–Haenszel proportions adjusted according to baseline clinical status.

† The P value was calculated from a Wilcoxon rank-sum test stratified by baseline clinical status.

‡ Clinical improvement was defined as an improvement of at least 2 points from baseline on the 7-point ordinal scale; recovery was defined as an improvement from a baseline score of 2 to 5 to a score of 6 or 7; and modified recovery was defined as an improvement from a baseline score of 2 to 4 to a score of 5 to 7 or from a score of 5 to a score of 6 or 7. Cumulative incidence functions were calculated for each treatment group for days to the event under evaluation (i.e., clinical improvement, recovery, or modified recovery), with death as the competing risk. Data for patients not achieving the event under evaluation at the last assessment were censored on the day of the last clinical assessment. Patients who died before achieving the event under evaluation were considered to have experienced a competing event.

1.death + 2. invasive MV/ECMO
5-day vs 10-day
16.0% vs 27.4%
OR=0.50 (95%CI：0.31-0.82)
p=0.006

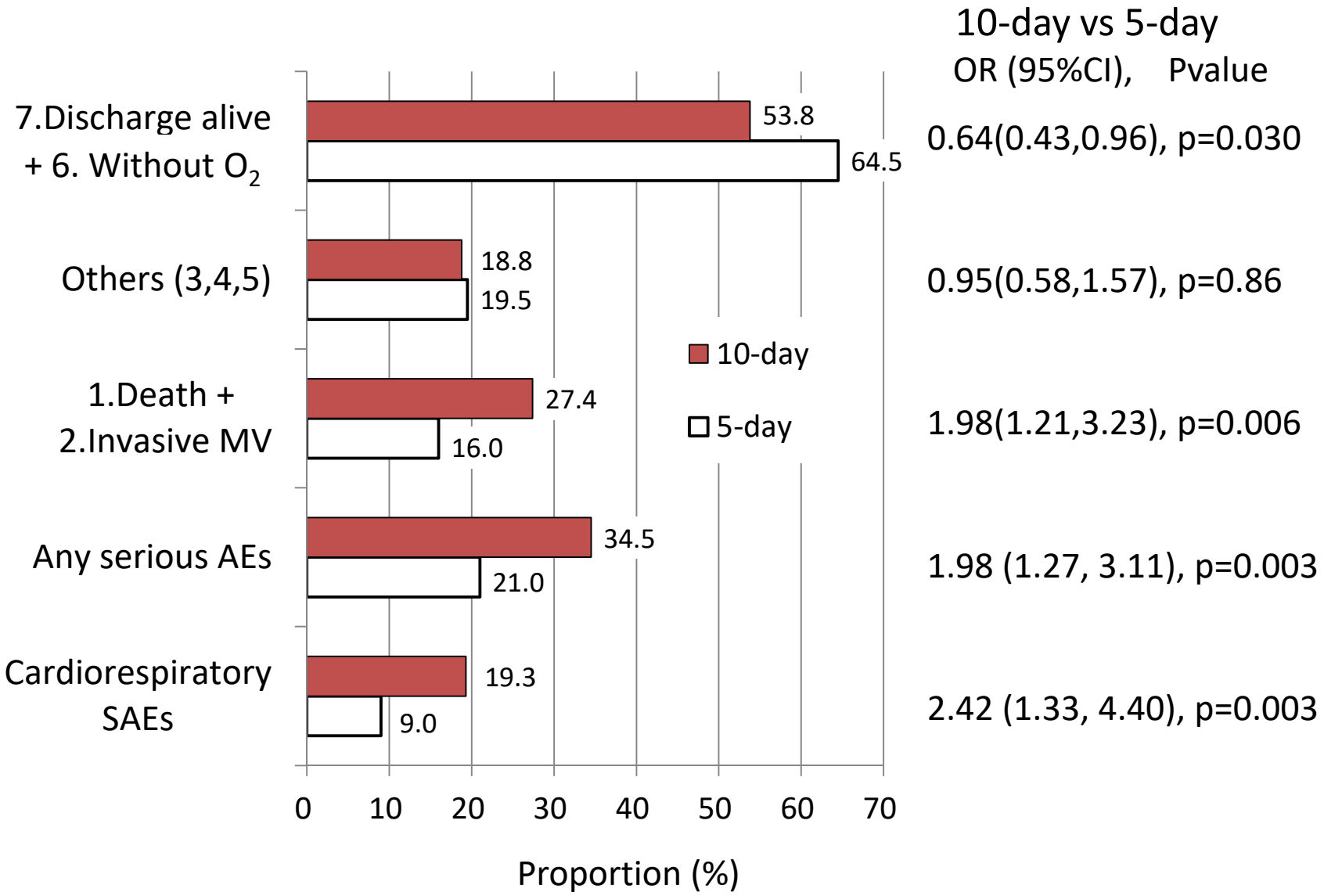
10-day vs 5-day
OR= 1.98 (1.28, 3.23)

5-day group improved better than 10-day group. Moreover, 5 day group died or become deteriorated less than 10-day group.

P=0.021
According to the Japanese label
Better outcome in 5-day group

SIMPLE trial（4） Results (2)：Main results

5-day group is significantly superior to 10-day group



SIMPLE trial (5)

Adverse events (AEs) And Serious AEs (SAEs)

Any SAEs double 10-day vs 5-day **OR=2.0 (1.3, 3.1), p=0.003**

Cardiorespiratory SAEs 10-day vs 5-day **OR=2.4 (1.3-4.4), p=0.003**

Table 3. Summary of Adverse Events According to Remdesivir Treatment Group.*

Event or Abnormality	5-Day Group (N=200)	10-Day Group (N=197)
Any adverse event — no. of patients (%)	141 (70)	145 (74)
Nausea	20 (10)	17 (9)
Acute respiratory failure	12 (6)	21 (11)
Alanine aminotransferase increased	11 (6)	15 (8)
Constipation	13 (6)	13 (7)
Aspartate aminotransferase increased	10 (5)	13 (7)
Hypokalemia	10 (5)	12 (6)
Hypotension	9 (4)	12 (6)
Respiratory failure	7 (4)	14 (7)
Insomnia	10 (5)	11 (6)
Acute kidney injury	4 (2)	15 (8)
Adverse event leading to discontinuation of treatment — no. of patients (%)	9 (4)	20 (10)
Any serious adverse event	42 (21)	68 (35)
Acute respiratory failure	10 (5)	18 (9)
Respiratory failure	5 (2)	10 (5)
Septic shock	2 (1)	5 (3)
Acute respiratory distress syndrome	1 (<1)	5 (3)
Hypoxia	2 (1)	4 (2)
Respiratory distress	3 (2)	4 (2)
Dyspnea	4 (2)	1 (1)
Pneumothorax	2 (1)	3 (2)
Viral pneumonia	3 (2)	2 (1)
Aminotransferase levels increased	3 (2)	2 (1)

SAEs were 2-fold more reported in 10-day group than 5-day group. Especially cardiorespiratory SAE（ARDS, (acute) respiratory failure, and septic shock) were 2.4-fold more frequently reported (p=0.003).