レムデシビル（商品名ベクルリー）COVID-19に無効の可能性が大きい

薬のチェック　編集委員会

2020.6.28

レムデシビルの作用機序(添付文書より要約)

・レムデシビルはプロドラッグ。
・体内で代謝されウイルス感染細胞内に入り、さらに代謝されて活性体となる。
・活性体はアデノシン三リン酸（ATP）の類似物質（偽物）。
・ウイルスのRNA依存性RNAポリメラーゼによりウイルスRNAが合成される際にはATPが取り込まれる。
・レムデシビルの活性体が、ATPと競合し（偽物として取り込まれ）、ウイルスRNA鎖が途中までしかできない。 基本的に、ファビピラビル（アビガン）の作用機序と同じ。

添付文書の記載

18. 薬効薬理

18.1 作用機序

レムデシビルはアデノシンヌクレオシドのプロドラッグであり、加水分解等による代謝を経て、ヌクレオシド類似体の一リン酸体となった後、細胞内に分布し、代謝されてヌクレオシド三リン酸型の活性代謝物を生成する。活性代謝物はアデノシン三リン酸（ATP）の類似体として、SARS-CoV-2 RNA依存性RNAポリメラーゼによって新たに合成されるRNA鎖に天然基質ATPと競合して取り込まれ、ウイルスの複製におけるRNA鎖の伸長反応を取り込みから少し遅れて停止させる。活性代謝物は、ヒト由来のDNAポリメラーゼα、β及びRNAポリメラーゼⅡ、並びにミトコンドリアDNAポリメラーゼγ及びミトコンドリアRNAポリメラーゼに対する阻害作用（IC_{50}値）はいずれも＞200μMであった。

18.2 *In vitro*抗ウイルス活性

レムデシビルは、SARS-CoV-2の臨床分離株に対して、薬剤添加48時間後におけるヒト初代培養気道上皮細胞での50%有効濃度（EC_{50}）は9.9nMであった。Vero細胞でのEC_{50}は、薬剤添加24時間後及び48時間後でそれぞれ137nM及び750nMであった。

動物実験（１） 症状が出た後では、効かない

エボラ、MERS、Nipah、SARS-CoV、SARS-CoV-2、いずれも動物実験で効果は証明されていない。

- すこしでも症状が出現した後で開始して死亡を減らしたという実験はなく、まして重症化後に開始して死亡を防止したという動物実験もない。
- 本来、**動物実験は、人での状況を再現して、効果が期待できるかどうかを知るために行うもの。**
- **しかし、レムデシビルの動物実験では、人でのウイルスの感染状況を考慮した実験は行われていない。**
- したがって、COVID-19の重症化後にレムデシビルを使用して効果があるかどうかは、動物実験でも確かめられていない。
- レムデシビルのすべての動物実験が、本来の実験方法になっていないのは、症状が出てから、しかも重症化してからでは、効果がほぼ期待できないことが分かっているから実験がなされていない、ということではないか。
- 動物実験を点検しよう。

動物実験(2):エボラウイルス

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

エボラウイルスをサルに注射、症状開始前に大量使用で死亡減。 しかし、症状発現後に投与した実験はなし。

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

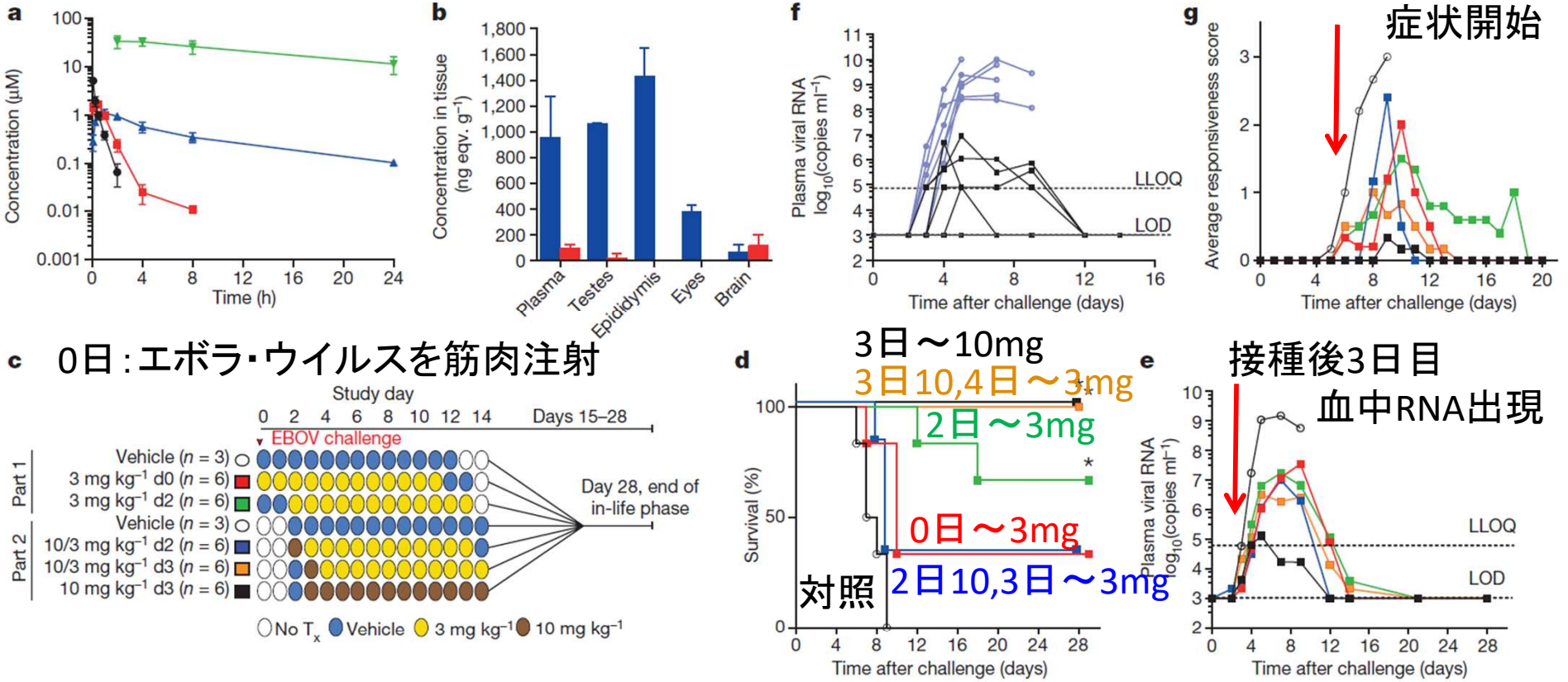


Figure 2 | GS-5734 pharmacokinetics and post-exposure protection against EBOV in rhesus monkeys. a, Pharmacokinetics following intravenous administration of 10 mg kg^{-1} GS-5734 dose in healthy rhesus macaques (mean ± s.d., $n = 3$). Plasma GS-5734 (black), alanine metabolite (red), and Nuc (blue); 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**).

動物実験(3):ニパウイルス

Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge

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

ニパウイルスをサルに注射、症状開始前（接種1日後）に大量使用で死亡減.
しかし、症状発現後に投与した実験はなし。

対照群の症状は3日後から

レムデシビルなしでは
8日目に全例が死亡

24時間後開始

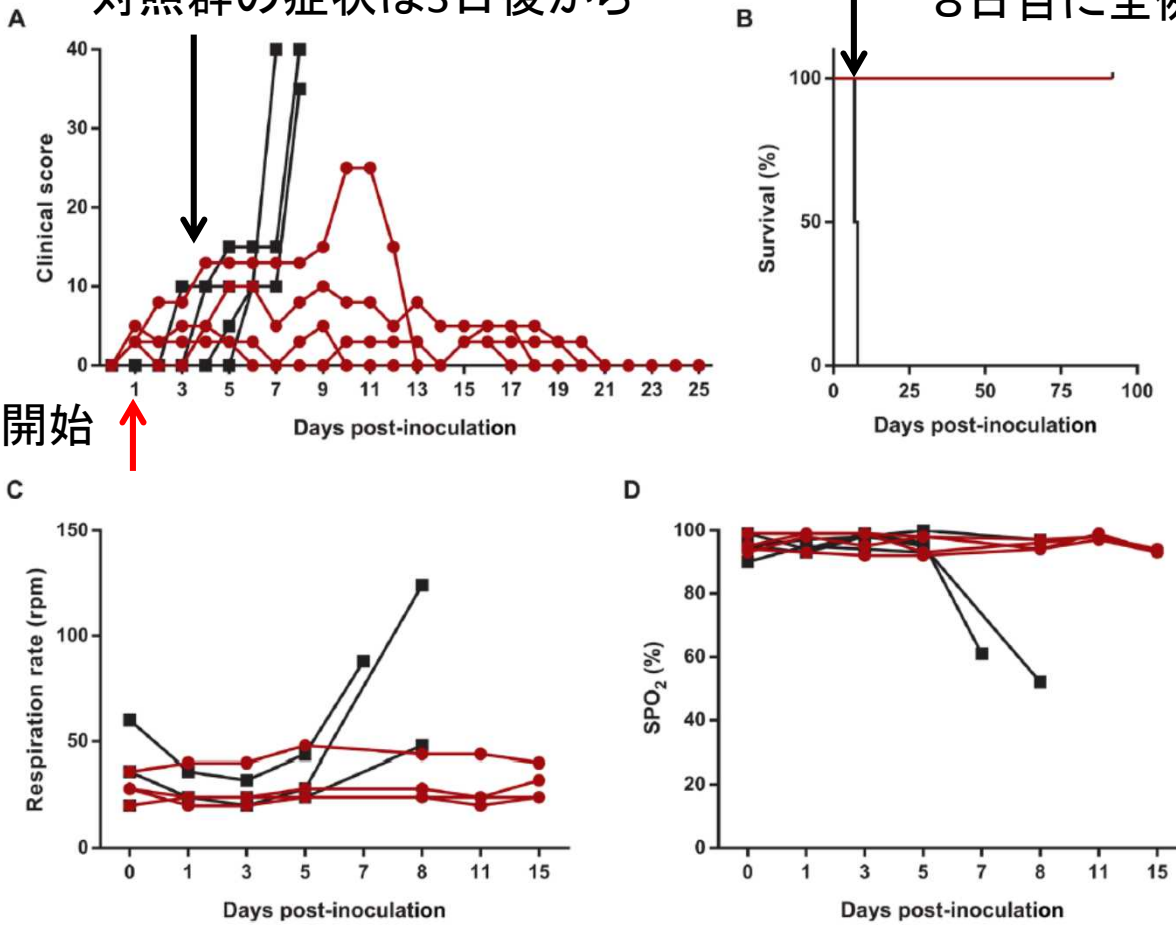


Fig. 1. Clinical signs in AGMs inoculated with a lethal dose of Nipah virus Bangladesh and treated with remdesivir. Two groups of four AGMs were inoculated intranasally and intratracheally with 10^5 $TCID_{50}$ of Nipah virus Bangladesh. At 1 dpi, the groups were treated intravenously with remdesivir (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.

動物実験(4)：MERSウイルス

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.

MERS ウイルス感染サルへのレムデシビルの予防的、治療的投与⇒ウイルス接種12時間後に開始で症状改善

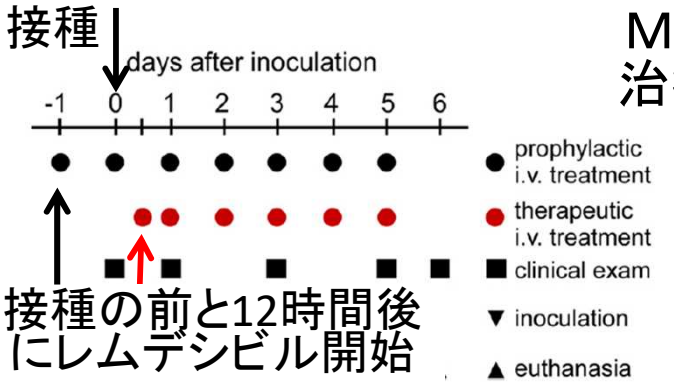
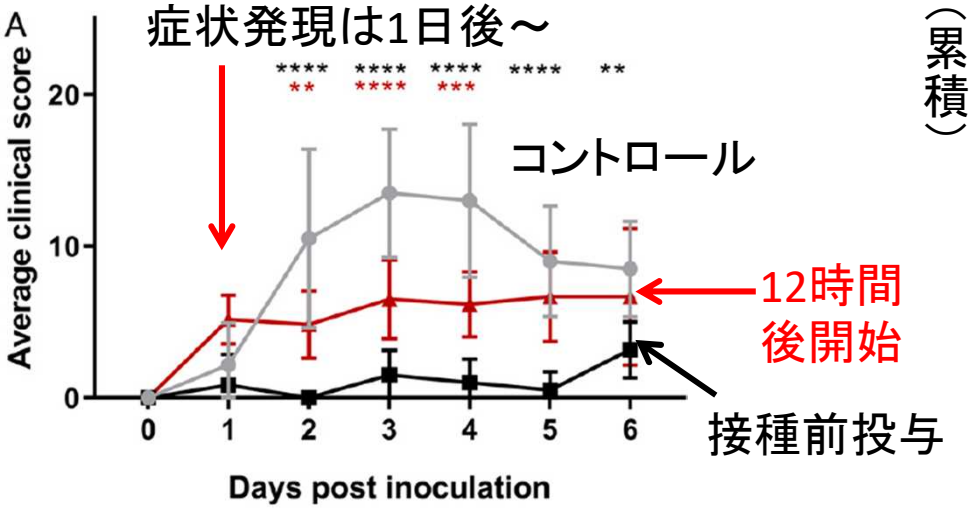
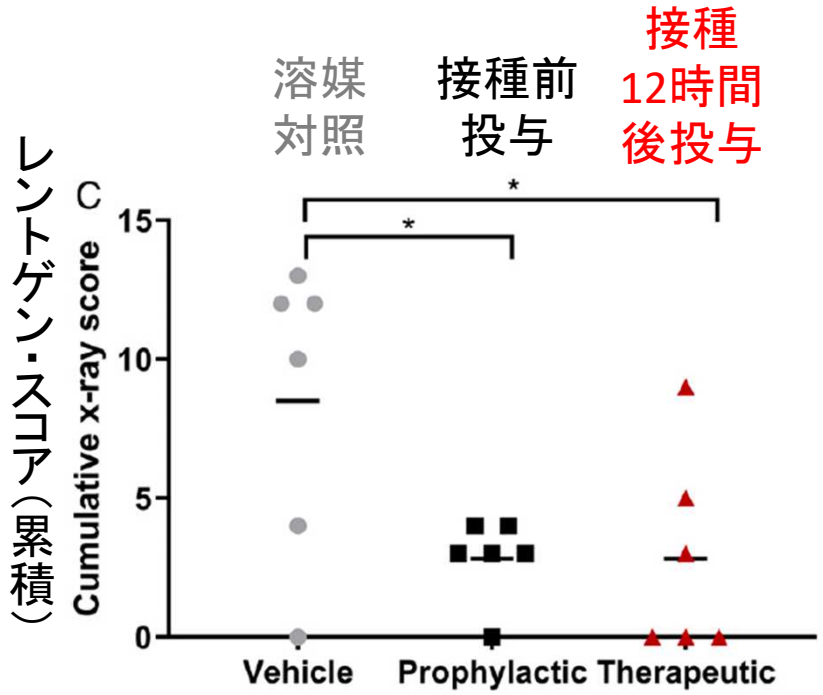


Fig. 1. Study outline. To test the prophylactic and therapeutic efficacy of remdesivir treatment in the rhesus macaque model of MERS-CoV infection, three groups of six rhesus macaques were inoculated with MERS-CoV strain HCoV-EMC/2012; one group was administered 5 mg/kg remdesivir starting at 24 h before 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.





動物実験(5)：SARSコロナウイルス感染マウスへのレムデシビル投与の効果

Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses

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

予防投与は接種の１日前、治療投与は接種1日後で症状軽減、しかし症状発現後に投与した実験はなし。

症状は2日目に出現

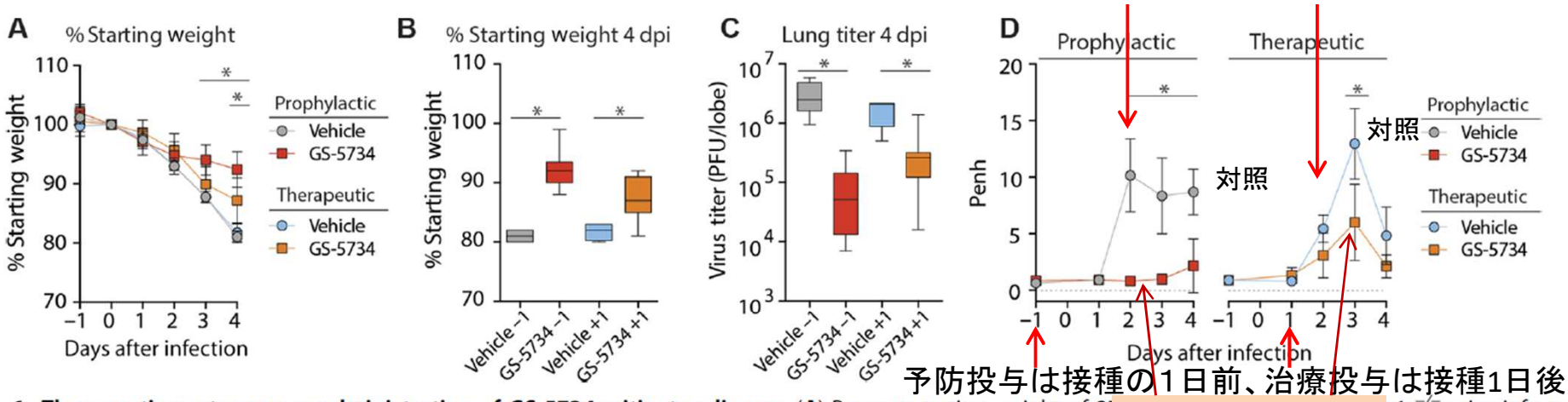


Fig. 6. Therapeutic postexposure administration of GS-5734 mitigates disease. (**A**) Percent starting weight of 27 *s1c*$^{-/-}$ mice infected with 10^3 PFU SARS-CoV MA15 and treated BID with vehicle or GS-5734 (25 mg/kg) beginning on either −1 dpi (vehicle, 1 dpi (vehicle, $n = 4$; GS-5734, $n = 11$). 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　これによって肺機能を測定（精度は高いとされる）

マウスに１日２回、25mg/kg＝50mg/kg=HED=4mg/kg

Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2

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

SARS-CoV-2を感染させたサルへのレムデシビルの治療的効果：やはり症状発現前の実験のみ

12時間後に投与開始

症状発現は24時間後

レントゲンスコア

Figure legends

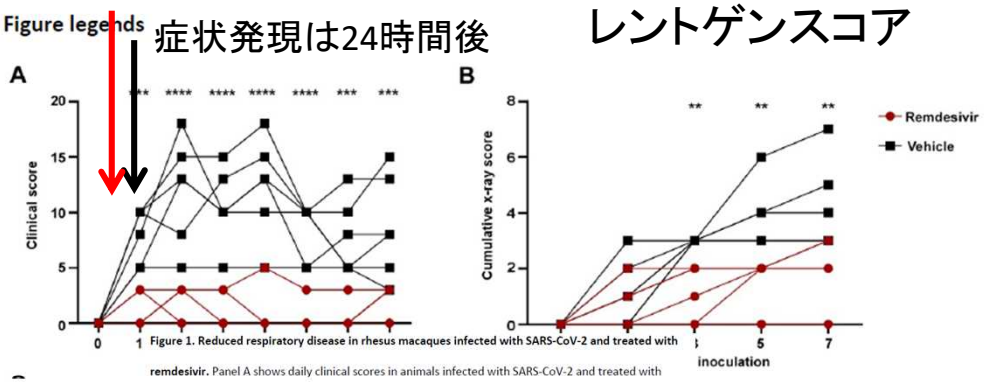


Figure 1. Reduced respiratory disease in rhesus macaques infected with SARS-CoV-2 and treated with remdesivir. Panel A shows daily clinical scores in animals infected with SARS-CoV-2 and treated with remdesivir (red circles) or vehicle solution (black squares). Panel B shows cumulative radiograph scores. Ventro-dorsal and lateral radiographs were scored for the presence of pulmonary infiltrates by a clinical veterinarian: 2: moderate 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

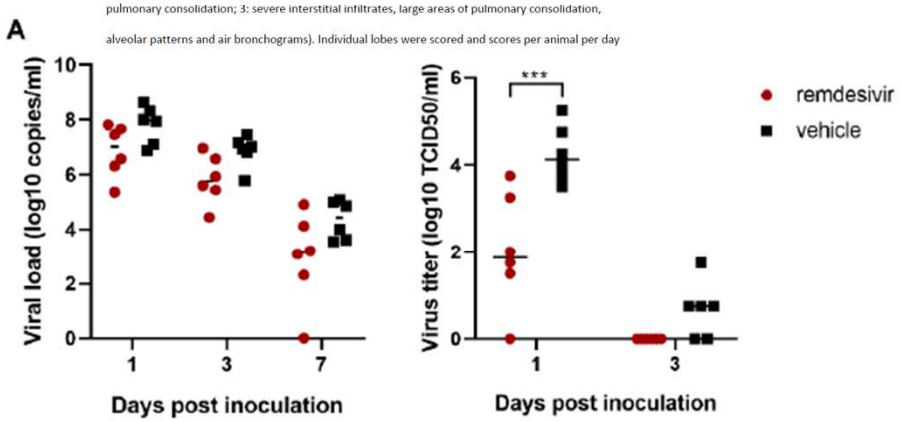
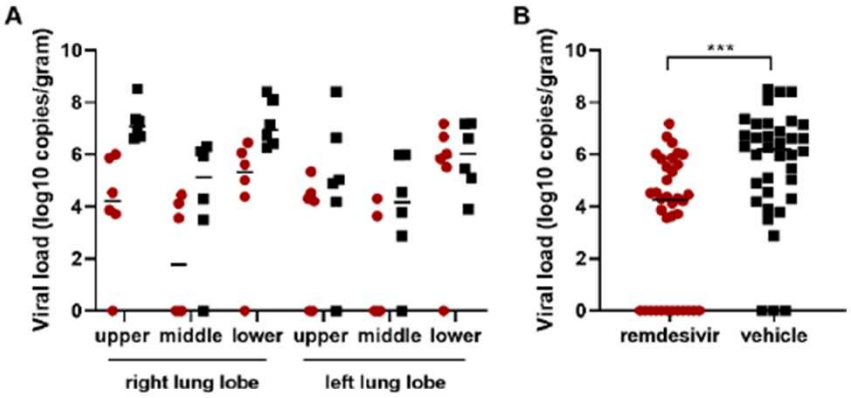


Figure 2. Viral loads and virus titers in bronchoalveolar lavage fluid. Panel A shows viral loads and Panel B shows infectious virus titers in BAL collected from rhesus macaques infected with SARS-CoV-2 and treated with remdesivir (red circles) or vehicle solution (black squares). Statistical analysis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



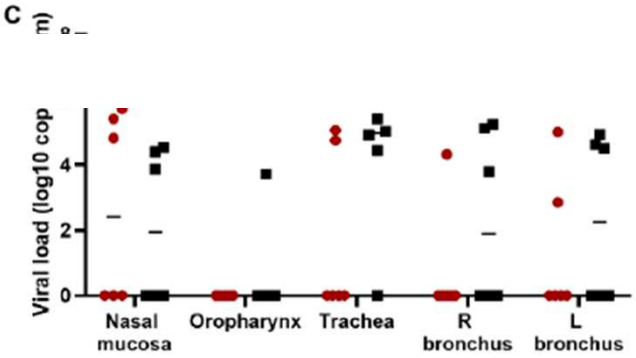


Figure 4. Viral loads in tissues collected from the respiratory tract on 7 dpi. Panel A shows viral loads in all six lung lobes collected from rhesus macaques infected with SARS-CoV-2 and treated with remdesivir (red circles) or vehicle solution (black squares), stratified per lung lobe. In panel B, 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.

しかも顕著な効果とはいえない

レムデシビルはエボラ治療剤ではない （1）

エボラ感染症に対するレムデシビルと 3種類のモノクローナル抗体との死亡率比較

A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics

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

死亡率　50%　53%　35%　34%

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

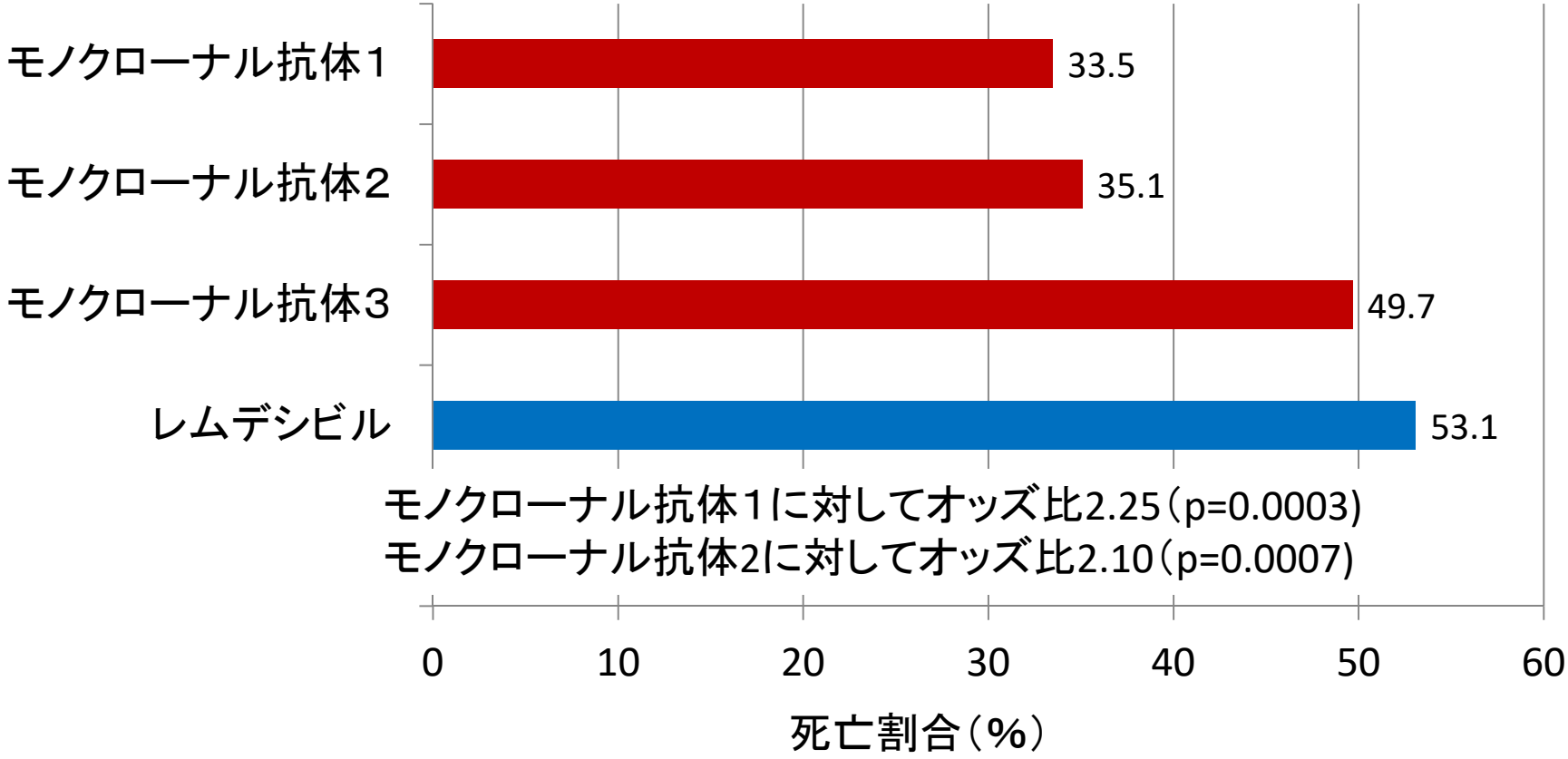
Population	ZMapp	Remdesivir	Difference, Remdesivir vs. ZMapp	MAb114	Difference, MAb114 vs. ZMapp	REGN-EB3	ZMapp Subgroup	Difference, REGN-EB3 vs. ZMapp Subgroup
	no. of deaths/ total no.(%)	*no. of deaths/ total no. (%)*	*percentage points (95% CI)*	*no. of deaths/ total no. (%)*	*percentage points (95% 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.

レムデシビルはエボラ治療剤ではない （2）

モノクローナル抗体よりもはるかに劣る

（死亡率が2倍超）



レムデシビルを使うと、2種類のモノクローナル抗体に比較して
死亡の危険度がオッズ比で2倍超（いずれも、p＜0.001）。

つまりレムデシビルはエボラ治療剤ではない。

レムデシビル特例承認の経過（まとめ）

日　付	実施主体	内容
4月23日	米国の医療関連ニュースサイトSTAT	WHOが公開したレムデシビル無効の情報をスクリーンショットとして報道 (速報No187参照)
4月29日	Lancet誌[10]	武漢RCT（プラセボ対照試験）NCT04257656の結果が報告された。
4月29日	米国立衛生研究所（NIH）	国立アレルギー・感染症研究所(NIAID)が主導するプラセボ対照試験(ACTT 試 験)[2] の 結論のみ公表（登録番号：NCT04280705）
4月29日	ギリアド・サイエンジズ（ギリアド社）	SIMPLE試験（重症例）の初期試験結果をプレスリリース
5月1日	米国規制当局（FDA)	緊急使用許可（EUA: Emergency Use Authorization)
5月4日	ギリアド社：	厚労省に承認申請
5月7日	薬事・食品衛生審議会医薬品第二部会	ウェブ会議形式で開催
5月7日	厚労省	レムデシビルの特例承認。世界初
5月22日 5月27日	NIAID主導ACTT試験 SIMPLE試験	NEJMにonline出版[11] NEJMにonline出版[12]

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*

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

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.

武漢RCT(1)

プラセボ対照試験

対象：
酸素吸入なしで酸素飽和度が94%以下など、ある程度以上重症で、
発症から12日以内のCOVID-19の患者237人。
時期：2月6日～3月12日までに登録された患者。
28日追跡し、
4月10日に終了。

登録が、3月13日以降なかったのは、武漢においてCOVID-19の患者発生がコントロールされてきたため（プロトコルの規定に従い試験への組み入れ中止のため）。

登録患者：
レムデシビル群158人、
プラセボ群78人
（1人は使用せず除外）

武漢RCT(2) 重症COVID-19に対するレムデシビルのプラセボ対照試験：主な背景因子

	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**

基本的に差なし

症状の程度
1.退院
2.入院中
酸素不要
3.入院中
酸素要
4.入院中
高用量酸素/
非侵襲人工呼吸
5.入院中
ECMOまたは
侵襲的人工呼吸
6.死亡

↓

アウトカム評価
にも使用

2段階改善
or 生存退院

気管挿管や気管切開をおこなって直接気道を確保し換気する**侵襲的人工換気**に対して，これら以外の方法でおこなわれる人工換気を非侵襲的人工換気と称する。この中で気道内圧を陽圧に保ちつつ，肺胞換気を補助する目的で，マスクを用いて陽圧をかける方法を**非侵襲的陽圧換気法（NIPPV）**と呼ぶ。
日本救急医学会、医学用語解説集より https://www.jaam.jp/dictionary/dictionary/word/0231.html

武漢RCT(3) 有意差ある背景因子

	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) 9,10日	71/155 (46%)	<	47 (60%)	P=0.037
Late (>10 days from symptom onset) 11,12日	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.

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

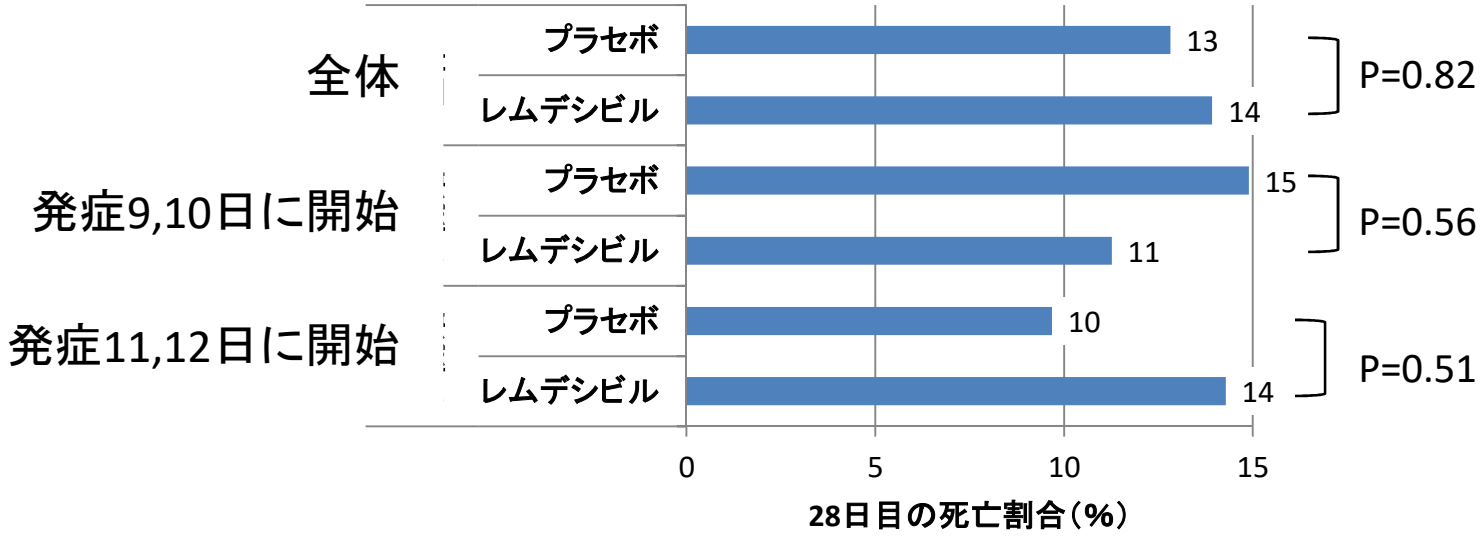
背景因子で唯一違いがあったのは発症から試験開始までの期間

その他は基本的に差なし

武漢RCT(4)　背景因子で差があった因子別の死亡率の比較

	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)

28日後死亡率
9,10日
11,12日

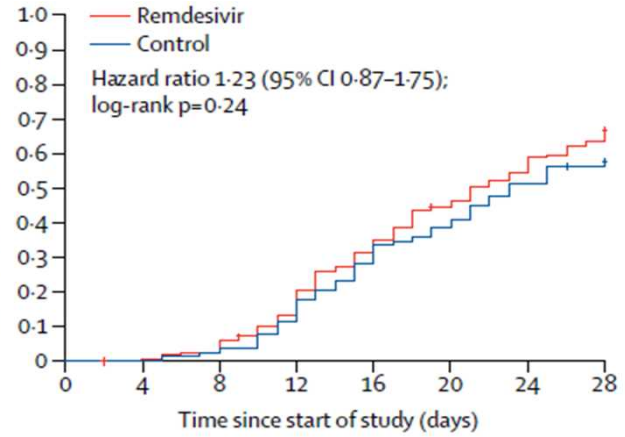


武漢RCT(5)：臨床的改善のカプランマイヤー曲線（ITT集団）

臨床的改善の定義：
臨床症状の
2段階以上改善
or　生存退院

臨床症状の程度
1.退院
2.入院中
酸素不要
3.入院中
酸素要
4.入院中
高用量酸素/
非侵襲人工呼吸
5.入院中
ECMOまたは
侵襲的人工呼吸
6.死亡

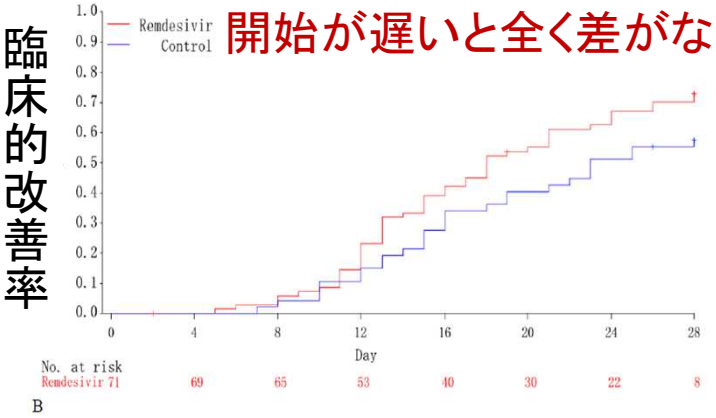
臨床的改善率



全体で
臨床的改善までの日数中央値
21日　vs　23日
臨床的改善までのハザード比：
1·23 (95% CI 0·87–1·75);

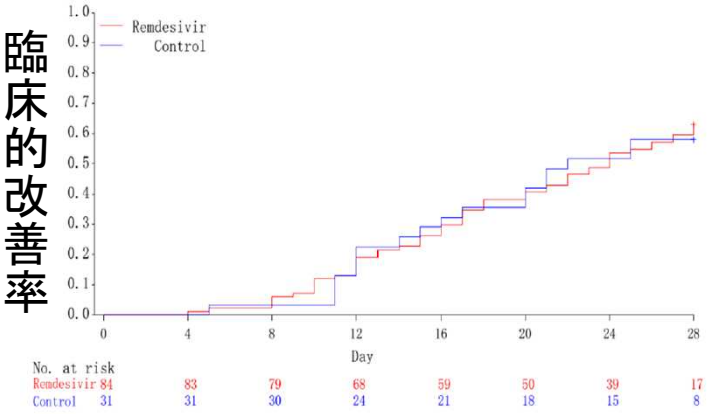
開始が遅いと全く差がないが、早めだと,よい傾向ありか？

臨床的改善率



(A)早期開始群（9日,10日目に開始）
臨床的改善までの日数中央値
18日　vs　23日
臨床的改善までのハザード比
1.52; 95%CI：0.95 - 2.43

臨床的改善率



(B)遅延開始群（11,12日目に開始）
臨床的改善までの日数中央値
23日　vs　24日
臨床的改善までのハザード比
1.07; 95% CI, 0.63 - 1.83

武漢RCT(6)：有害事象

	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

有害事象は基本的に差がない

重篤有害事象

	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

武漢RCT(7)：試験中止に至る有害事象

	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%)

呼吸不全/ARDS　p=0.20

重篤な有害事象

	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)

試験中止に至る有害事象中
呼吸不全/急性呼吸窮迫症候群(ARDS)
という、COVID-19の中心的症状が
レムデシビル群に多い傾向があった。
これは何を意味するのか？

武漢RCT(8)：上気道で陽性であった例の累積陰性化の割合

ウイルス量の変化

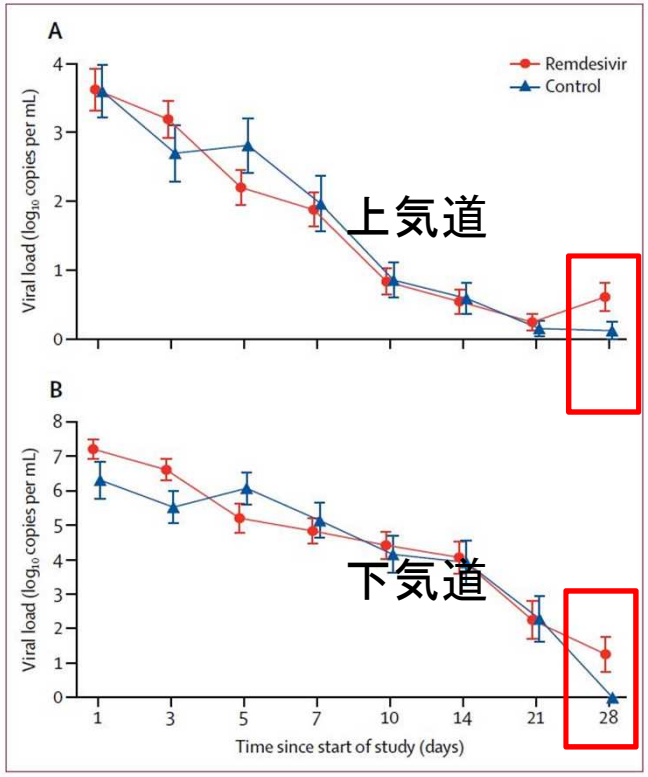


Figure 3: **Viral load by quantitative PCR on the upper respiratory tract specimens (A) and lower respiratory tract specimens (B)**
Data are mean (SE). Results less than the lower limit of quantification of the PCR assay and greater than the limit of qualitative detection are imputed with half of actual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

第3～4週に、レムデシビルでウイルス消失が遅れる傾向あり
特に生存者で、10%近い違いは何を意味するのか？これも矛盾

Table S2. Accumulated rate of undetectable viral RNA in upper respiratory tract specimens in viral positive population. %が小さいほど、ウイルス消失が遅れる

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試験（1）基本情報

Condition or disease	Intervention/treatment	Phase
COVID-19	Other: Placebo Drug: Remdesivir	Phase 3

Study Design

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	800 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Double (Participant, Investigator)
Primary Purpose:	Treatment
Official Title:	A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of **COVID-19** in Hospitalized Adults
Actual Study Start Date :	February 21, 2020
Estimated Primary Completion Date :	April 1, 2023
Estimated Study Completion Date :	April 1, 2023

Arm

Placebo Comparator: Placebo

200 mg of Remdesivir placebo administered intravenously on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir placebo while hospitalized for up to a 10 days total course. n=286.

Experimental: Remdesivir

200 mg of Remdesivir administered intravenously on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir while hospitalized for up to a 10 days total course. n=286.

Adaptive：早期の終了や、中間解析の結果に基づいて、途中で試験デザインの変更を可能にする試験方法：適応的デザインによる臨床試験

ACTT試験：米国国立研究機関が主導した、プラセボ対照ランダム化比較試験（RCT)

ACTT：**Adaptive COVID-19 Treatment Trial**

添付文書：論文のサマリーの内容とほぼ同じ

17．臨床成績
17.1 有効性及び安全性に関する試験
17.1.1 使用経験
(1) NIAID ACTT-1試験（NCT04280705）

18歳以上のSARS-CoV-2による感染症患者を対象としたプラセボ対照無作為化二重盲検並行群間比較試験において、投与初日に本剤200mgを、2～10日目に本剤100mgを1日1回静脈内投与した。なお、退院した場合は投与を中止することとされた。主要評価項目は、無作為化後28日目までにおける回復までの時間であった。1,063例が1：1の割合で本剤群又はプラセボ群に割り付けられ、606例の回復例が得られた時点で実施された主要評価項目等に関する予備的解析の結果は、回復までの時間の中央値は、本剤投与群で11日、プラセボ群で15日であった（ハザード比：1.31、95%信頼区間：1.12～1.54、p<0.001）。死亡割合は、本剤投与群で8.0%、プラセボ群で11.6%であった（p=0.059）。なお、本試験の主な選択・除外基準は下表のとおりであった。

当初は、開始後29日目の予後で判定する予定としたが、対象者数が急速に増えたので、15日目の予後で判定することに変更した。その結果、4月27日の予備解析（中間解析）で、上記添付文書記載の結果が得られた。

ACTT試験（2）中間解析

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

Remdesivir for the Treatment of Covid-19 — Preliminary Report

for the ACTT-1 Study Group Members*

5月22日公表されたACTT試験
Abstractは添付文書の内容とほぼ同じ

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%).

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

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.)

ACTT試験（3）

Figure 1.
ACTT試験：
組み入れと
ランダム化
流れ図

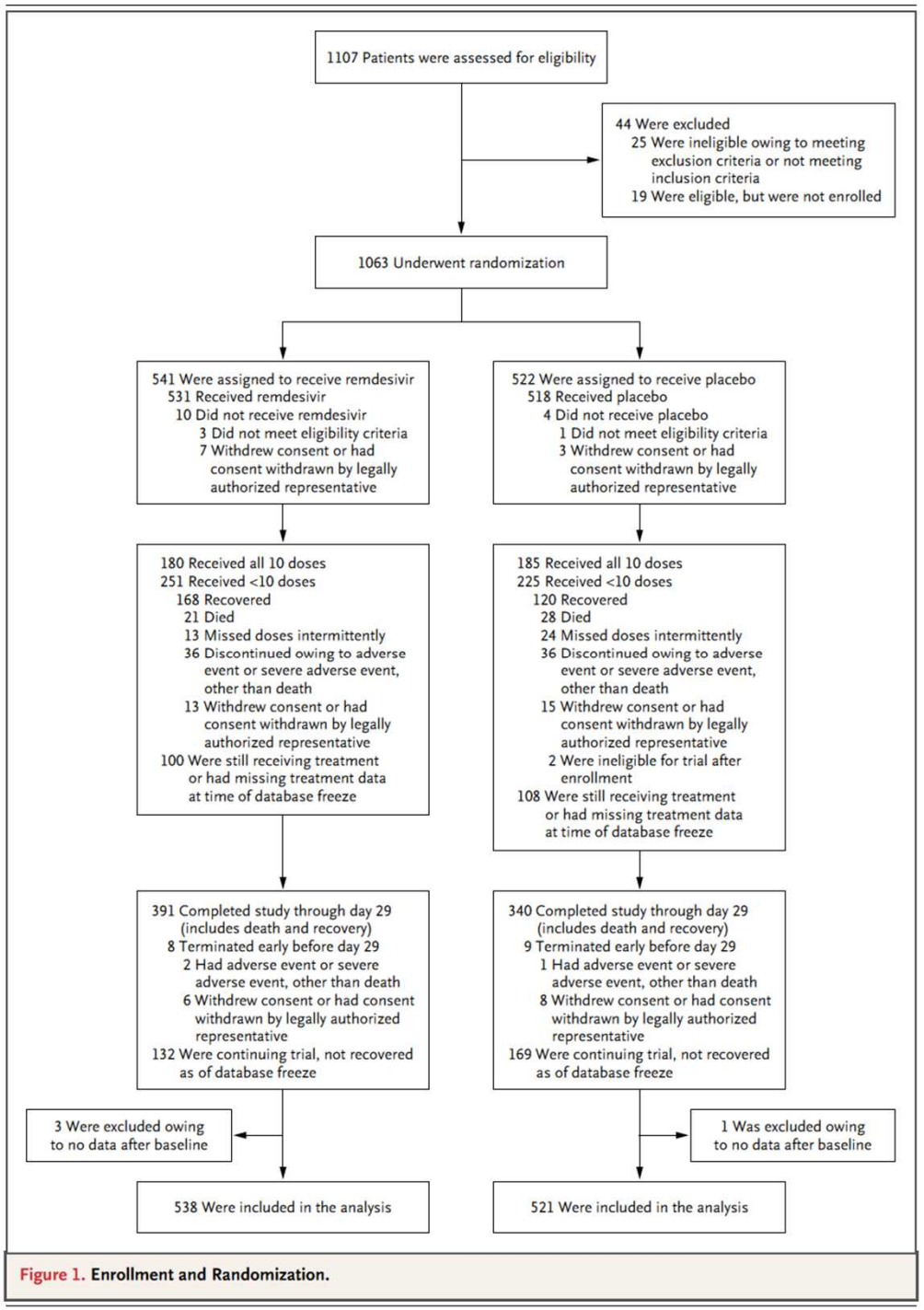


Figure 1. Enrollment and Randomization.

ACTT試験（4）背景因子

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.

23% vs 28%
P＝0.059

ACTT試験（5）Fig. 2　累積回復率：試験開始時の重症度別カプラン-マイヤー推定値

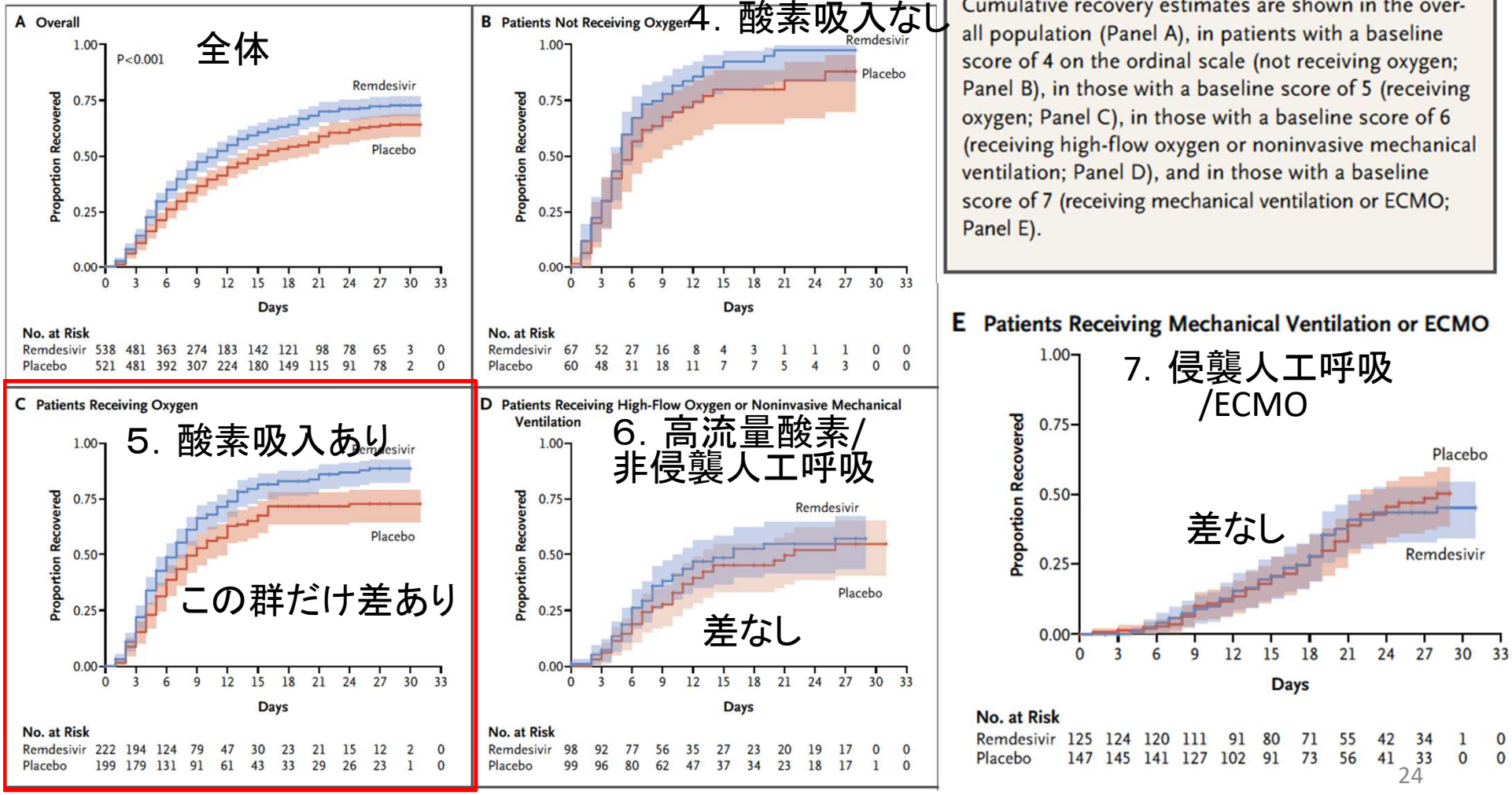


Figure 2 (facing page). Kaplan–Meier Estimates of Cumulative Recoveries.

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試験（6）

ベースラインのスコア

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

	Overall*		4. 酸素なし		5. 酸素吸入		6. 高酸素		7. 侵襲MV	
	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)	

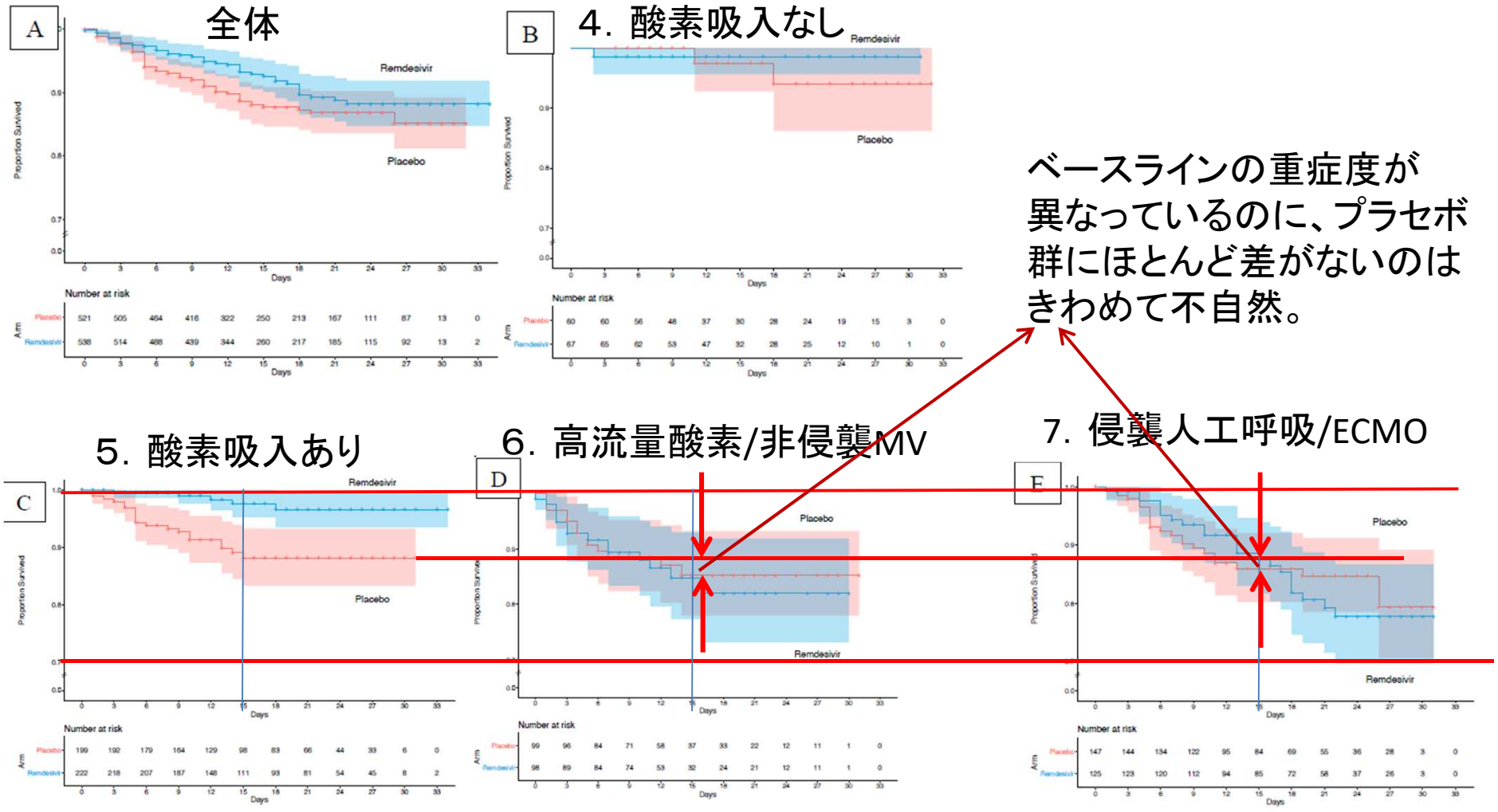
* P values and confidence intervals have not been adjusted for multiple comparisons. NE denotes not possible to estimate.

† 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.

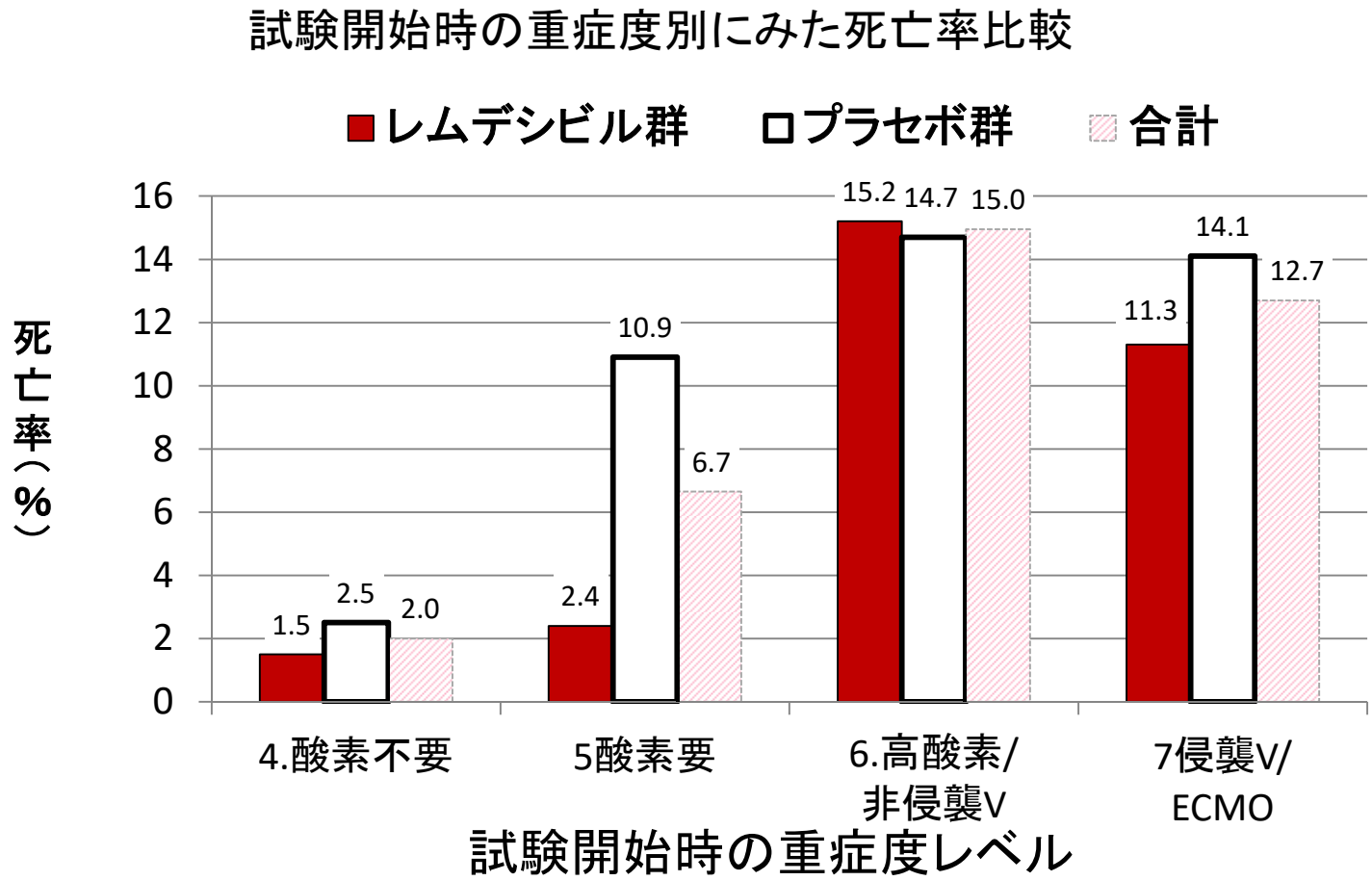
ACTT試験（7） ベースラインの重症度別生存曲線

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.



5.群のプラセボ群と、重症（6,7群）のプラセボ群の生存率に差がないのは不自然！！

ACTT試験（8）：14日目死亡率の比較（カプラン・マイヤー推定値）



試験開始時の重症度がレベル4群（酸素不要）、レベル6群（高流量酸素または非侵襲性人工呼吸器装着）、レベル7群（侵襲性人工呼吸器装着）では、レムデシビル群■とプラセボ群□の死亡率に差はなく、レベル5群（酸素吸入を要する例）でのみ差があった。
レムデシビル群のレベル5群死亡率（2.4%）はレベル4群（1.5%）に近く、プラセボ群のレベル5群の死亡率（10.9%）はレベル6群（15.2%）やレベル7群（11.3%）にむしろ近く、レベル5群のみ、有効である理由は見出しがたく、他の重症度群の結果と矛盾している。[27]

ACTT試験（9） ACTT試験中間解析段階での評価

- 背景因子として、試験開始前の重症度レベル7が、p=0.059と有意に近い違いがあったが、それ以外は、大きな背景因子の違いはなかった。
- 開始時重症度別に、臨床症状の改善や、生存率を比較すると、レベル４、６，７では全く差がなく、差があったのはレベル５（酸素吸入要）のみであった。
- レベル5では、プラセボ群の死亡率が著しく高く、レベル６やレベル7と有意差なく、５，６，7を用いたトレンド分析でも有意でなかった。
- 一方、レベル5のレムデシビル群の死亡率が著しく低く、レベル4とまったくと言ってよいほど差がなかった。
- レムデシビル群とプラセボ群を合計すると、レベル5の死亡率は、レベル4とレベル6,7とのちょうど中間となり、生物学的に極めて妥当と考えられる死亡率となった。
- 以上を総合すると、試験開始時にレベル5であった421人のプラセボ群、レムデシビル群への割り付けが適切であったかどうか疑問がある。
- 試験開始時にレベル5であったプラセボ群199人、レムデシビル群222人の背景因子の詳細（例えば、ランダム化直前の酸素分圧ないし酸素飽和度の分布の比較、クレアチニン値、AST,ALTなど重症度に関係する検査値の分布の比較）が明らとなり、これらの背景因子に差がないことが確認されない限り、この試験結果は信頼できないと考える。

SIMPLE試験 （1） 査読論文出版前の段階での情報

5日使用と、10日使用での比較試験（プラセボ群なし）

添付文書の記載

(2) GS-US-540-5773試験 (NCT04292899)

12歳以上18歳未満かつ体重40kg以上、及び18歳以上のSARS-CoV-2による重症感染症患者を対象とした無作為化非盲検並行群間比較パートにおいて、5日間投与群では、投与初日に本剤200mgを、2～5日目に100mgを1日1回静脈内投与、10日間投与群では、投与初日に本剤200mgを、2～10日目に100mgを1日1回静脈内投与した。なお、退院した場合は投与を中止することとされた。いずれの投与群も標準療法の併用を受けた。主要臨床評価項目は、無作為化後14日目に順序尺度[注1)]で評価した臨床状態とされた。臨床状態の改善について、5日間投与群に対する10日間投与群のオッズ比は0.76［95%信頼区間0.51，1.13］であった。

また、5日間投与群及び10日間投与群でそれぞれ、50%の患者が退院するまでの時間は10日及び11日、14日目において、臨床状態の2段階以上の改善[注2)]が認められた患者の割合は65%（129/200例）及び54%（107/197例）、回復[注3)]が認められた患者の割合は70%（140/200例）及び59%（116/197例）、死亡の割合は8%（16/200例）及び11%（21/197例）であった。

ギリアド社プレスリリース(4/29) 5日群, 10日群

	n=200	n=197	p-value[1]
Clinical Efficacy Outcomes at Day 14			
≥ 2-point improvement in ordinal scale	129 (65)	107 (54)	0.16
Clinical recovery	129 (65)	106 (54)	0.17
Discharge	120 (60)	103 (52)	0.44
Death	16 (8)	21 (11)	0.70
Safety			
Any adverse event (AE)	141 (71)	145 (74)	0.86
Grade ≥3 study drug-related AE	8 (4)	10 (5)	0.65
Study drug-related serious adverse event (SAE)	3 (2)	4 (2)	0.73
AE leading to discontinuation	9 (5)	20 (10)	0.07

[1]Adjusted for baseline clinical status

	5日使用(n=200)		10日使用(n=197)	オッズ比	p値	調整p値
2段階改善	129人 (65%)	vs	107人 (54%)	1.53	0.039	0.16
回復	**140人 (70%)**	**vs**	**116人 (59%)**	**1.63**	**0.021**	**示されず**
回復の定義: 酸素吸入を要しない又は退院した場合						
退院	120人 (60%)		103人 (52%)	1.37	0.12	0.44
有害事象で中止	9人 (5%)	vs	20人(10%)	0.42	0.030	0.07
呼吸不全で中止	**12人 (6%)**	**vs**	**21人(11%)**	**0.53**	**0.093**	示されず

SIMPLE試験 （2）

ORIGINAL ARTICLE

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

Jason D. Goldman, M.D., M.P.H., David C.B. Lye, M.B., B.S., David S. Hui, M.D., 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試験 （3）

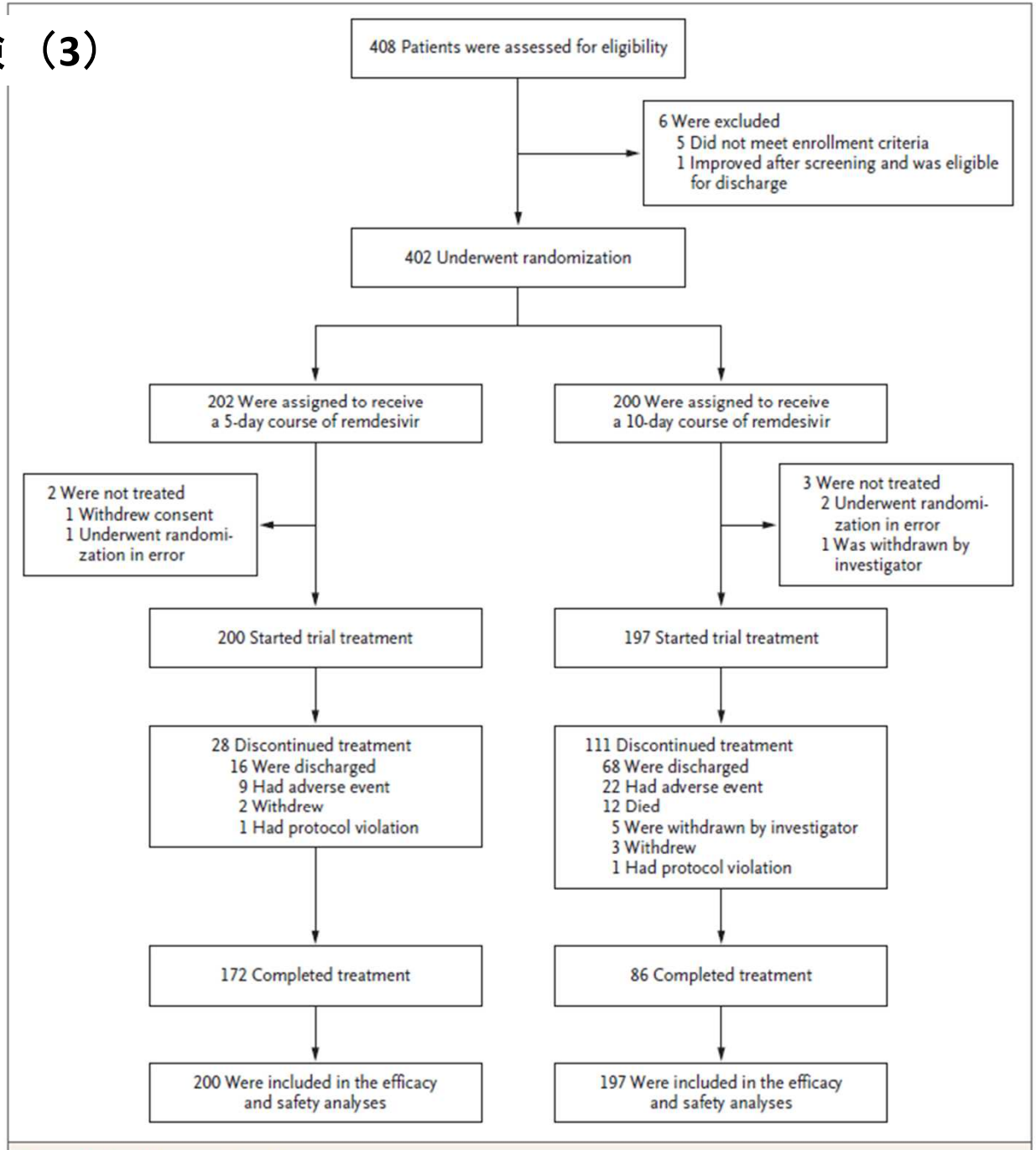


Figure 1. Enrollment and Randomization.

SIMPLE試験 （4）

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試験（5）結果

5日群が10日群より症状の回復が速く、

しかも、死亡・重症状態になるのが有意に少ない。

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.

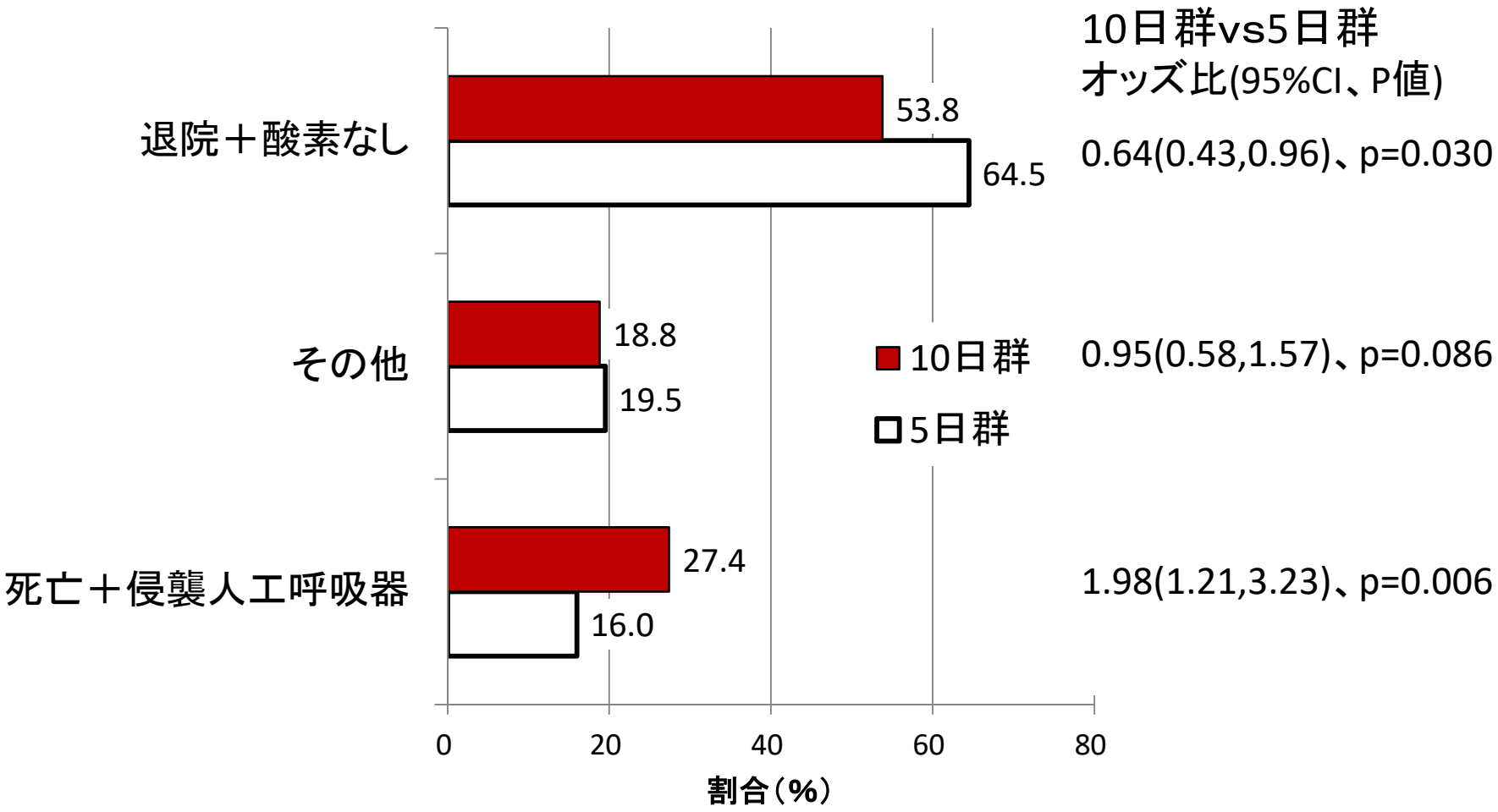
‡ Clinical improvement was defined as an improvement of at least 2 points from baseline on the 7-point ordinal scale; recovery was defined as an improvement from a baseline score of 2 to 5 to a score of 6 or 7; and modified recovery was defined as an improvement from a baseline score of 2 to 4 to a score 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.

14日目の死亡と侵襲人工呼吸器/ECMO装着を合わせた患者の割合は、16.0%対27.4%
オッズ比=0.50
95%CI：0.31-0.82、
p=0.006

添付文書記載の回復
P=**0.021**

SIMPLE試験（6） 結果（その2：主要な結果）

５日使用群が10日使用群よりも優れる



SIMPLE試験（7）

重篤有害事象
が2倍
（p=0.003）

呼吸不全系
重篤有害事象
は、**2.4**倍
（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)

重篤有害事象も10日群が5日群よりも約2倍多く（p=0.003）、
特に呼吸不全関連重篤有害事象（ARDS、急性呼吸不全、
敗血症性ショック）の合計は2.4倍（p=0.003）

(2) GS-US-540-5773試験（NCT04292899）

なお、本試験の主な選択・除外基準は下表のとおりであった。

主な選択・除外基準

選択基準	1. 無作為化前4日以内に実施したPCR検査においてSARS-CoV-2感染が確認されている 2. 入院中 3. スクリーニング時に、SpO_2が94%以下（室内気）又は酸素吸入を要する 4. 画像上、肺浸潤影が認められる
除外基準	1. 多臓器不全 2. 人工呼吸器（V-V ECMOを含む）を5日間以上使用、又はV-A ECMOを使用（使用期間を問わない） 3. ALT又はASTが基準範囲上限の5倍超 4. クレアチニン・クリアランスが50mL/min未満（18歳以上の場合はCockcroft-Gault式、18歳未満の場合はSchwartz式を用いて算出） 5. 妊娠検査陽性 6. 授乳中

害反応にも注意が必要

- 害反応として、特に注意が必要なのは、腎機能障害が悪化するおそれ。
- 添付文書には、「添加物の尿細管への蓄積により、腎機能障害が悪化するおそれがある。」「非臨床試験でレムデシビルに腎尿細管への影響が認められている。」と記載されている。
- 腎障害のほか、肝障害や、低血圧（血圧低下）、嘔気、嘔吐、発汗、振戦、各種血液検査値、血液化学検査値などの変化も記載されている
- これらは、COVID-19の症状そのものの悪化でも起こりうることであり、レムデシビルによる害なのか、現病の悪化なのか、区別が困難なことが考えられる。

プラセボ対照試験がますます困難になる

- 英国医師会雑誌（BMJ）の最近のEditorial[6]
  https://www.bmj.com/content/369/bmj.m1610　では、
  「比較のない観察研究で時間を浪費してはいけない」と、
  プラセボ対照の比較試験の重要性を強調。
- *「十分な規模の、目隠しが適切に行われたランダム化比較試験が実施されてはじめて、確実な結果が得られる。現在、レムデシビルに関して登録されている臨床試験が少なくとも23件あり、合計23,500人の患者が対象となっているが、二重遮蔽試験は4分の1にも満たず、中には対照をもたない観察研究もある。」*
- Natureのeditorial（2020-5-13)でも同様の論調
  https://www.nature.com/articles/d41586-020-01391-9
- 今回のように、一旦、承認してしまうと、あたかも安全性と効力が確認されたかのように受け止められ、プラセボを対照としたランダム化比較試験が「非倫理的」であるかのように誤解されて、まっとうな臨床試験の実施はますます困難になってきます。

日本の再評価は何時になるのか

- レムデシビルの承認は「特例承認」[3]であり、承認に際して猶予された資料に関して「提出の猶予期間は、承認取得から起算して9ヶ月」とされ、「提出された資料等により、承認事項を変更する必要が認められた場合には、承認事項の変更を命ずることがある」とはされている。
- しかし、その一方、「再審査期間は8年」とされており、よほどのことがない限り、承認は長期に及ぶ可能性がある。

結論

- レムデシビルの感染動物を用いた実験や、メーカーによる臨床試験のデザインは、いずれも効力証明のために適切に計画されたものでない。
- このことから、レムデシビルのCOVID-19に対する効力と安全性が証明される見込みは、今後とも極めて少ないと考える。
- まず、症状発症後にレムデシビルを投与するCOVID-19の感染動物実験で死亡減少が証明される必要がある。
- そのうえで、厳密に管理された適切な規模のプラセボ対照試験をヒトで実施すべきである。
- そのプラセボ対照試験で、効力と安全性が証明されない限り無効と考え、使用しないようにすべきである。